Paper No. _____

Filed on behalf of: Party Raz

By: Oliver R. Ashe, Jr., Esq.
Azy S. Kokabi, Esq.
ASHE, P.C.
11440 Isaac Newton Sq. North
Suite 210
Reston, VA 20190
Tel.: (703) 467-9001
Fax: (703) 467-9002
E-mail: oashe@ashepc.com
akokabi@ashepc.com

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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EYAL **RAZ**
Junior Party
(U.S. Patent 6,498,148),

v.

ARTHUR M. **KRIEG** and JOEL KLINE
Senior Party
(U.S. Application 09/337,584).

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Patent Interference 105,526 (MPT)
(Technology Center 1600)

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# RAZ OPPOSITION 4

(Opposing Krieg Contingent Responsive Motion to Add New Claims 104 and 105)

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# RAZ OPPOSITION 4

## I. OVERVIEW

Krieg Contingent Responsive Motion ("Krieg Motion 4") contingently moves to add new claims 104 and 105 to U.S. Patent Application No. 09/337,584 to Krieg et al ("the involved '584 Krieg application") in the event that either of Raz Motions 1 or 3 is granted. The Board should either dismiss or deny the relief requested in Krieg Motion 4 for at least the following reasons:

- Krieg Motion 4 fails to comply with the procedural requirements set forth in the Rules and the Standing Order;
- Krieg Motion 4 fails to establish that claim 104 satisfies the written description and enablement requirements of 35 U.S.C. § 112, first paragraph;
- Krieg Motion 4 fails to establish whether the provisions of 35 U.S.C. § 135(b)(1) are applicable to claim 104. If applicable, Krieg Motion 4 fails to rebut the presumption that claims 104 and 105 are unpatentable to Krieg under 35 U.S.C. § 135(b)(1); and
- Krieg Motion 4 fails to establish that claims 104 and 105 interfere with Raz's Involved Claims.

Accordingly, Raz respectfully submits that the Board should either dismiss or deny Krieg Motion 4.

## II. THE EVIDENCE

Appendix 1 sets forth a list of exhibits, papers, and appendices upon which Raz relies in support of this Opposition. SO ¶ 122.4.1.

## III. STATEMENT OF MATERIAL FACTS

Appendix 2 sets forth each material fact alleged in Krieg Motion 4 and Raz's corresponding concise response. Appendix 3 sets forth additional material facts upon which Raz relies in support of this Opposition. SO ¶ 122.4.2.

## IV. A SIGNIFICANT NUMBER OF KRIEG'S STATEMENT OF FACTS ARE IMPROPER AND REFLECT INADMISSIBLE EVIDENCE

A significant number of Krieg's facts are in violation of the Standing Order (Paper No. 2) and the Federal Rules of Evidence governing hearsay. Specifically, Standing Order ¶ 152.2.1 states:

> A specification of an involved application or patent is admissible as evidence only to prove what the specification or patent describes. If there is data in the specification upon which a party intends to rely to prove the truth of the data, an affidavit by an individual having first-hand knowledge of how the data was generated (i.e., the individual who performed an experiment reported as an example in the specification) must be filed. This individual may be cross examined.

In particular, at least facts 47, 48, 72, 74, 75, 86, 88, 89, 91, 93-99 are inadmissible under Standing Order ¶ 152.2.1 and Fed. R. Evid. 801 and 802. In each of these facts, Krieg has relied solely upon the data presented in the specification of the Krieg involved application to prove the truth of the matter asserted, without providing the required affidavit by an individual having first-hand knowledge of how the data was generated. For example, Krieg has stated, in Fact 72: "[t]he data in the Krieg application, including those presented in Tables 1-3, **establish** that CG nucleic acids are immunostimulatory." (Emphasis added). Similarly, Fact 74 states that "[t]he data presented in Tables 5 and 13 **demonstrate** that CG nucleic acid stimulate a Th1 response profile in human cells also." (Emphasis added). Clearly, Krieg is improperly attempting to

prove the "truth" of what the data in the Krieg specification demonstrates, in violation of the prohibition against hearsay and in contravention of the Standing Order.

Accordingly, at least the above-recited facts should be not be relied upon by the Board and should be excluded from consideration in accordance with Standing Order ¶¶ 152.2.1; 121.5.2 and the Federal Rules of Evidence.

## V. ARGUMENT

### A. Procedural Requirements For A Responsive Motion To Add A Claim

The rules governing interference proceedings clearly set forth the burden of proof associated with a responsive motion to add a new claim to a moving party's application. First, 37 C.F.R. § 41.121(a)(2) defines a responsive motion to add a claim to cure a defect raised in a substantive motion. 37 C.F.R. § 41.121(b) squarely places on the moving party the burden of establishing that it is entitled to the requested relief. 37 C.F.R. § 41.208(c) states that a party moving to add a claim must show that the claim is patentable.

The provisions of the Standing Order set forth additional requirements that must be satisfied by a party seeking to add a claim to its involved application. ¶ 208.5.1 of the Standing Order states that a motion to add a claim must:

- show the written description for the claim in the disclosure of the involved application to which it would be added;
- certify that the movant is not aware of any reason why the claim is not patentable; and
- explain why a patentability problem raised in a motion is overcome by the proposed claim.

As explained below, Krieg Motion 4 fails to comply with the procedural and substantive requirements set forth in the interference rules and the Standing Order and, therefore, should be either dismissed with prejudice or denied.

**B. Krieg's Proposed New Claims Lack Written Description under 35 U.S.C. § 112, first paragraph**

On page 2, lines 4-8, Krieg suggests that it has satisfied the requirements of ¶ 208.5.1 of the Standing Order and 37 C.F.R. § 41.110(c)(2) by providing a claim chart in Appendix 4 of its Motion. Furthermore, on page 11, lines 6-9, Krieg suggests that proposed claims 104 and 105 overcome the arguments raised in Raz Motions 1 and 3 by again referring to a claim chart in Appendix 4 of its Motion.

**Raz's response** is that Krieg has failed to satisfy its burden of establishing that it is entitled to the relief requested in Krieg Motion 4. Krieg Motion 4 provides no explanation of how the claim chart in Appendix 4 demonstrates that any of the involved Krieg specifications satisfy the written description requirement with respect to claim 104. Krieg Motion 4 does not cite to any evidence to establish that one of ordinary skill in the art would have considered Krieg to be possession of the full scope of its claimed invention.

Notably, ¶ 208.5.1 of the Standing Order states that "if a claim is added to overcome a patentability problem raised in a motion, the motion to add the claim must explain why the proposed claim would overcome the problem." 37 C.F.R. § 41.121(e) further provides that "[c]laim charts are not a substitute for appropriate argument and explanation in the paper."

Raz Motion 1 established that Krieg's involved claims are so broad that they encompass methods of treating asthma by administering an immunostimulatory polynucleotide sequence without administering an antigen as part of the treatment. *See*, Facts 128 and 131. Raz Motion 1

established that one of ordinary skill in the art reading Krieg's involved specification would not have considered Krieg to have described such a method of treating asthma. *See*, Facts 131 and 132

Krieg Motion 4 is utterly devoid of any argument or explanation of how, in view of the Board granting Raz Motion 1 on grounds of lack of written description, proposed claim 104 overcomes the lack of written description established by Raz. Appendix 4 is not a substitute for the requisite explanation in Krieg's Motion. Krieg has plainly failed to satisfy its burden of establishing that proposed claim 104 satisfies the written description requirement and, hence, is patentable to Krieg.

At page 6, lines 7-9, Krieg states "Krieg claim 104 is silent with respect to whether an antigen is administered. (Fact 45). Krieg claim 104 therefore encompasses administering the nucleic acid with or without an antigen. (Fact 46)." At page 17, lines 9-10, Krieg states "the scope of Krieg claim 104 is not materially different from the scope of Krieg claim 44..." At page 17, lines 18-19, Krieg concludes "[t]hus, the scope of Krieg claim 104 is the same or substantially the same as the scope of Krieg claim 44."

**Raz's response** is that Krieg appears to be expressly admitting that Krieg claim 104 suffers from the same lack of written description as the Board will have found rendered unpatentable Krieg's involved claims, *i.e.*, that none of Krieg's specifications teach a method of treating asthma by administering an immunostimulatory nucleic acid without administering an antigen as part of the treatment. In fact, the statements made in Krieg Motion 4 remove any doubt that Krieg claim 104 suffers the same written description deficiencies as Krieg claim 44 and Krieg's other involved claims. Not only does Krieg Motion 4 fail to explain how proposed

claim 104 overcomes the unpatentability established in Raz Motion 1, Krieg expressly admits that it does not.

Having failed to establish that Krieg claim 104 satisfies the written description requirement of 35 U.S.C. § 112, first paragraph, Krieg is (at best) left with Krieg claim 105, which does not interfere with any of Raz's claims for the reasons explained herein. *See*, Facts 135 and 137. This is precisely the point underlying Raz's Motion 2 alleging no interference-in-fact, *i.e.*, that Krieg is, at most, only entitled to claims for treating asthma ***requiring*** the administration of antigen.

Significantly, when presented with an opportunity to present claims which it considers to have written description in its specifications, Krieg elected to introduce one claim that is "silent" with regard to the administration of antigen (claim 104) and one claim that expressly requires the administration of antigen (claim 105). *See*, Facts 129-130, 134, and 137. Notably, Krieg did not present a claim that is commensurate in scope with Raz's involved claims (*i.e.*, expressly excluding the administration of antigen as part of the method of treating asthma), even though Krieg is presently attempting to secure allowance of such claims in *ex parte* prosecution outside of this interference in U.S. Patent Application No. 10/743,625. *See*, Facts 129-130, 134, and 140-142. Krieg's failure to move to add such a claim in response to Raz's substantive motions should be construed as a disclaimer of such subject matter. *See In re Ogiue,* 517 F.2d 1382, 1390, 186 U.S.P.Q. 227, 235 (C.C.P.A. 1975) (refusal to add claim to permit interference treated as concession).

Furthermore, to the extent that Krieg is attempting to redefine the subject matter it considers to be its invention in terms of a treatment of an "allergy," rather than the treatment of "asthma," Krieg's arguments still fail. The Krieg specification contains a single bald statement

that "an effective dose of an immunostimulatory nucleic acid (or a vector containing a nucleic acid) alone or in conjunction with an allergen can be administered to a subject to treat or prevent an allergy." *See*, Facts 160-161. As already stated in Raz's Motions, there are no data or experiments disclosed in the involved Krieg '584 application which show that an ISS alone, administered without antigen, was sufficient to treat or prevent allergy, much less asthma. *See*, Fact 162. As discussed below, Krieg's published reports squarely refute any suggestion that Krieg had observed any immunological effect by administering an ISS without the antigen. *See*, Facts 227-251.

Accordingly, Krieg has failed to establish that proposed claim 104 overcomes the patentability problems raised by Raz Motion 1.

**C. Krieg's Proposed New Claims are Not Enabled**

On page 11, line 10 to page 15, line 4, Krieg argues that claims 104 and 105 are enabled by the involved Krieg specification.

**Raz's response** is that Krieg fails to satisfy its burden of proving that proposed claim 104 overcomes the lack of enablement established in Raz Motion 1.

Raz Motion 1 establishes that Krieg's specification does not enable the full scope of Krieg claim 44 because Krieg's specification would not have enabled one of ordinary skill in the art to practice a method of treating asthma by administering an immunostimulatory polynucleotide without administering an antigen as part of the treatment. *See*, Facts 131-132.

As noted above, Krieg states in Motion 4 that the scope of Krieg claim 104 is the same or substantially the same as the scope of Krieg claim 44. If Krieg claim 104 is of the same scope as Krieg claim 44 and the Board finds Krieg claim 44 unpatentable for lack of enablement, then Krieg claim 104 suffers from the same patentability defect as Krieg claim 44 and should not be

added to Krieg's application. Therefore, Krieg Motion 4 is fundamentally flawed because it fails to show the patentability of Krieg claim 104 and fails to explain how Krieg claim 104 overcomes the patentability problems raised in Raz Motion 1.

Krieg Motion 4 fails to establish enablement of Krieg claim 104 for additional reasons.

On page 13, lines 10-14, Krieg states:

> The Krieg application further demonstrates that CG nucleic acids induce their Th1 effects independent of antigen administration. (Fact 90). *In vivo* experiments in mice show that CG nucleic acids induce a Th1 cytokine profile even when administered without antigen or allergen. (Fact 91). CG nucleic acids therefore induce a Th1 immune profile *in vivo* even when antigen is not administered to a subject. (Fact 92).

**Raz's response** is that Krieg's observations do not establish that proposed claim 104 is enabled with respect to a method of treating asthma by administering an immunostimulatory polynucleotide without the administration of an antigen.

First, in reaching Krieg Motion 4, the Board will have already determined that the above-cited disclosure is not adequate to enable the full scope of Krieg claim 44. In view of the concession that Krieg claim 44 and proposed claim 104 are of identical scope with regard to the administration of antigen as part of the claimed treatment, proposed claim 104 would suffer the same lack of enablement as Krieg claim 44.

Second, at best, the above-cited disclosures establish that a Th1 cytokine profile can be induced using an immunostimulatory polynucleotide without the administration of an antigen. Krieg claim 104 is directed to a method of treating asthma, not a method of inducing a Th1 cytokine profile. *See*, Fact 13 and 133. Krieg's witness, Dr. Wallner, testified that an animal model for asthma must be used to evaluate a method of treating asthma, not sole reliance on a cytokine profile. *See*, Fact 172. As explained by Krieg's other witness, Dr. Center, the so-called

"Th1 cytokines" are not necessarily exclusive to a Th1 response because the cytokines can be produced by non-Th1 cells. *See*, Facts 170 and 173. Moreover, Dr. Center testified that the mere presence of Th1 cytokines does not demonstrate that a shift from a Th2 to a Th1 immune response has occurred. *See*, Fact 170.

On page 13, lines 15 to 17, Krieg states that "Example 12 confirms that a CG nucleic acid would have the ability to initiate *in vivo*, **even in the presence of an antigen**, a pattern of cytokine release which would drive the immune system toward a Th1 response and would treat asthma." (Emphasis added). On page 14, lines 8-11, Krieg states that "[b]ased upon these teachings [of Example 12], one of ordinary skill in the art would have concluded that CG nucleic acids would bias the immune system toward Th1, **even when administered with an antigen that otherwise would provoke a Th2 response.** (Fact 100)." (Emphasis added).

**Raz's response** is that Krieg's misleading assertions are egregious.

By stating that Example 12 demonstrates an effect "even in the presence of an antigen" and "even when administered with an antigen that otherwise would provoke a Th2 response" Krieg is implying that one of ordinary skill in the art would have first understood that Example 12 somehow implicitly taught that asthma could be treated by the administration of an immunostimulatory polynucleotide without the administration of an antigen. Nothing could be farther from the truth, and Krieg knows it. *See*, Facts 146-155.

First, by reaching Krieg Motion 4, the Board will have already determined that Example 12 provides neither written description nor enablement for Krieg claim 44. Therefore, it is futile for Krieg to rely on the same example for support of a claim that is admittedly identical in scope with respect to the claim limitation involving administration of an immunostimulatory polynucleotide without the administration of an antigen.

Second, to the extent Example 12 leaves any room for speculation about Krieg's ability to treat asthma without the administration of antigen, such room for speculation was created by material omissions from the disclosure in Example 12. *See*, Fact 150. As noted in Raz Motion 1, in publications commensurate in scope with Krieg Example 12, Krieg repeatedly reported that the administration of an immunostimulatory polynucleotide ***without*** the administration of an antigen did ***not*** result in immune responses indicative of a treatment of asthma. *See*, Facts 227-251. For example, in September 1996, Drs. Kline and Krieg, the named inventors on the involved Krieg application, published an Abstract titled "CpG Motif Oligonucleotides are Effective in Prevention of Eosinophilic Inflammation in a Murine Model of Asthma" ("the Kline '96 Abstract"). *See*, Fact 227. The Kline '96 Abstract describes an experiment wherein ISS was administered "alone." *See*, Facts 231-232. In particular, the Kline '96 abstract says, **"[s]ystemic administration of the oligonucleotide,...<u>alone</u> did not result in any significant change in BAL cellularity..."** (Emphasis added). *See*, Fact 232. Additionally, in 1997, Drs. Kline and Krieg published another Abstract titled "Immune Redirection by CpG Oligonucleotides: Conversion of a Th2 Response to a Th1 Response in a Murine Model of Asthma" ("the Kline '97 Abstract"). *See*, Fact 234. The Kline '97 Abstract reported that **"CpG ODN co-administered with *Schistosome* eggs (<u>but not CpG ODN alone</u>) lead to decreased airway eosinophilia following subsequent airway challenge with SEA."** *See*, Fact 240; Emphasis added. Finally, Kline et al. published a Paper titled "Cutting Edge: Modulation of Airway Inflammation by CpG Oligodeoxynucleotides in Murine Model of Asthma" ("the Kline '98 Paper") that was received for publication on November 26, 1997, and accepted for publication on January 14, 1998. *See*, Fact 242. The Kline '98 Paper reported that **"CpG ODN <u>alone</u> do not offer significant**

**protection against the development of airway inflammation.**" *See*, Fact 248; Emphasis added.

Notably, in the Kline '98 Paper, Krieg expressly noted the authors' conclusion that the methods described in the publication (and, likewise, in Example 12 of Krieg's applications) were antigen-specific. *See*, Fact 250. Krieg Motion 4 provides no explanation of how an example that teaches a method of treating asthma without administration of an antigen could be antigen-specific.

Despite these numerous statements in Krieg's published literature indicating that administering CpG alone was ineffective for the treatment of asthma, Krieg did not include such statements in Example 12. *See*, Facts 147-157 and 227-250. Yet, it is this very omission upon which Krieg now urges the Board to find its claim 104 patentable.

Indeed, the Board should note that during prosecution of Krieg's involved U.S. Patent Application No. 09/337,584, the Examiner specifically noted that "Example 12 teaches that CpG and the SEA [an antigen] were administered to the asthmatic subject at the same time" and that it "is not clear from the example shown if the CpG administered alone to an asthmatic will redirect the cytokine responses and therefore Th1 type immune responses." *See*, Fact 138. In response to the rejection, Krieg coyly stated that "[n]othing in Example 12 suggests that the use of CpG oligonucletoides alone as therapy for asthma does not work." *See*, Fact 139. Of course, Example 12 did not contain such a suggestion because Krieg omitted from Example 12 his published statements to the contrary. *See*, Facts 147-154.

**D. Krieg Is Not Entitled to Benefit of the '774 or '652 Applications Under 35 U.S.C. § 120 and Claim 104 is Therefore Unpatentable Over Prior Art**

On page 15, lines 5-21, Krieg argues that proposed claims 104 and 105 overcome the unpatentability of Krieg's involved claims as established in Raz Motion 3. On page 15, lines 13-17, Krieg asserts that its previously filed '774 and '652 applications also fully support proposed claims 104 and 105.

**Raz's response** is that, as previously established herein, Krieg's arguments are without merit. Krieg has admitted that Krieg claim 104 is identical in scope to Krieg claim 44 with respect to the administration of an immunostimulatory polynucleotide without the administration of an antigen. Krieg Motion 4 is contingent on the Board finding that Krieg claim 44 lacks written description and enablement with regard to such embodiments. Accordingly, Krieg has failed to explain how proposed claim 104 overcomes the patentability problem raised in Raz Motion 3. Krieg is not entitled to the benefit of its earlier-filed applications and, therefore, claim 104 is unpatentable under 35 U.S.C. § 102(b) in view of published PCT application WO 98/18810. *See*, Facts 174-201.

**E. Krieg's Certification Is Deficient**

On page 10, lines 13-14, Krieg certifies that "it is not aware of any reason why claims 104 and 105 are not patentable to Krieg."

**Raz's response** is that Krieg's certification appears to be deficient. At page 6, lines 7-9, Krieg Motion 4 states that "Krieg claim 104 is silent with respect to whether an antigen is administered. (Fact 45). Krieg claim 104 therefore embraces administering the nucleic acid with or without an antigen. (Fact 46)." On page 2, line 9, to page 8, line 4, Krieg extensively argues that Krieg claim 104 would anticipate or render obvious Raz claim 17 and *vice-versa*. See also,

page 9, line 1 to page 10, line 10, wherein Krieg considers the designation of claim 104 as corresponding to a Count defined by Raz claim 17.

Based on Krieg's representations, Krieg clearly considers the subject matter of Raz claim 17 to be a significant part of the subject matter encompassed by Krieg claim 104. Applying Krieg's rationale, a rejection of a Krieg claim that is commensurate in scope with Raz claim 17 would appear to be relevant to the patentability of Krieg claim 104.

Krieg substantially copied Raz claim 17 in Krieg's presently pending U.S. Patent Application No. 10/743,625 ("the '625 application"). *See*, Facts 140-142. Krieg's claim has been repeatedly rejected by the *ex parte* Examiner and remains rejected as being unpatentable to Krieg. *See*, Facts 143-144. Nevertheless, Krieg Motion 4 does not mention the existence of the '625 application, much less the various rejections of claims which Krieg Motion 4 urges are squarely within the scope of Krieg claim 104.

Although the '625 application is not an involved benefit file, in accordance with the *principles* set forth in Standing Order ¶ 208.5.1, Krieg's certification should be accorded no weight. SO ¶ 208.5.1 ("A certification that is inconsistent with the prosecution history of an involved or benefit file will be accorded no weight unless the inconsistency is explained."), *see also* Fact 141. Krieg has not explained how proposed claim 104 is patentable while all of Krieg's claims 19-39 of the '625 application stand rejected.

### F. Krieg Failed To Conduct a Proper Analysis of the Patentability Of Its Claims Under 35 U.S.C. § 135(b)(1)

On page 16, line 1 to page 18, line 5, Krieg argues that proposed claims 104 and 105 comply with the requirements of 35 U.S.C. §§ 135(b)(1) and (2). At page 16, lines 17-18, Krieg concedes that proposed claims 104 and 105 are being made more than one year after the issuance

of the Raz patent. On page 16, line 18 to page 17, line 8, Krieg argues that proposed claims 104 and 105 are nonetheless patentable under 35 U.S.C. § 135(b)(1) because previously presented claims 60 and 76 "are claims of the same or substantially the same scope" as proposed claims 104 and 105. At page 17, lines 6-8, Krieg concludes that "Claims 104 and 105 therefore are directed to the same or substantially the same subject matter as claims 60 and 76, and at least for this reason are not barred under 35 U.S.C. § 135(b)(1)."

**Raz's response is** that Krieg fails to address the fundamental step in evaluating the applicability of 35 U.S.C. § 135(b)(1). Section 135(b) is relevant to "[a] claim that is the same as or for the same or substantially the same subject matter as, a claim of an issued patent." Therefore, section 135(b) requires a comparison of the claim made by the applicant (*i.e.*, claim 104 and 105) against an issued patent claim (*e.g.*, Raz claim 17) to determine whether either of proposed claims 104 and 105 is the same as or for the same or substantially the same subject matter as, a Raz '148 patent claim (*e.g.*, Raz claim 17). Krieg has failed to conduct such an analysis, and therefore, Krieg's arguments are deficient on their face.

Assuming that the Board determines that Krieg's proposed claims 104 and 105 are for the same or substantially the same subject matter as the involved Raz patent claims (which Krieg has not established), Krieg's claims 104 and 105 are materially different in scope from Krieg's claims 44, 60, and 76, and thus are not entitled to an earlier effective date. *See*, Facts 202-206.

On page 16, lines 17-22, Krieg asserts that claims 104 and 105 are the same or substantially the same as claims 60 and 76 which were pending prior to the Critical Date.

**Raz's response is** that Krieg's claims 104 and 105 are not "the same as" claims 60 and 76. *See*, Facts 203 and 205-207. Moreover as explained below, claims 104 and 105 are not for the same or substantially the same subject matter as claims 60 and 76 because claims 104 and 105

contain material limitations not present in claims 60 and 76 and vice versa. *See Regents of the Univ. of California v. Univ. of Iowa Research Found.*, 455 F.3d 1371, 79 U.S.P.Q.2d 1687 (Fed. Cir. 2006) ("we find the difference in scope and subject matter of claims 202 and 203 from claim 205 to be indicative of inventions that are not substantially the same.").

Below, Krieg's claims 60 and 76 are compared to Krieg claims 104 and 105:

| Krieg claims presented on October 2, 1999 | Krieg Proposed New Claims |
|---|---|
| 60. A method for desensitizing a subject against the occurrence of an allergic reaction in response to contact with an allergen, comprising administering to a subject an effective amount for desensitizing the subject against the occurrence of an allergic reaction of an immunostimulatory nucleic acid, having a sequence including at least the following formula:<br>5' $X_1$ $X_2$CG$X_3$ $X_4$ 3'<br>wherein C is unmethylated, wherein $X_1X_2$ and $X_3X_4$ are nucleotides, wherein at least one nucleotide has a phosphate backbone modification. | 104. A method for treating asthma comprising<br>administering to a subject with hypersensitivity to an allergen that includes an asthmatic response an effective amount for treating asthma of an immunostimulatory nucleic acid, having a sequence including at least the following formula:<br>5' $X_1X_2$ CG $X_3X_4$ 3'<br>wherein C is unmethylated, wherein $X_1X_2$ and $X_3X_4$ are nucleotides, wherein the nucleic acid has a length of 8 to 100 nucleotides. |
| 76. The method of claim 60, further comprising administering an allergen to the subject. | 105. The method of claim 104, further comprising administering an allergen to the subject. |

### *1. "Asthma" and "Allergic Reaction" Are Materially Different In Scope and Subject Matter*

Proposed claims 104 and 105 are directed to a method of treating "asthma," whereas claims 60 and 76 are directed to a method of desensitizing a subject against the occurrence of "an allergic reaction."

Krieg's witness (Dr. Wallner) and Raz's witness (Dr. Schleimer) agree that "an allergic reaction" is a generic term that one of ordinary skill in the art would recognize as not commensurate in scope with "asthma" and that broadly refers to a large number of different

syndromes. *See*, Facts 208-209. Both witnesses also agree that one of ordinary skill in the art would understand that allergic asthma is one of several allergic conditions that would fall within the scope of an "allergic response." *See*, Facts 207-209. Therefore, one of ordinary skill in the art would understand that a claim reciting "asthma" is materially different in scope from a claim reciting "an allergic reaction." *See*, Facts 205-209. Therefore, claims 104 and 105 are materially different (in terms of scope and subject matter) from claims 60 and 76 and are presented by Krieg to overcome the unpatentability of Krieg's Involved Claims. Assuming the provisions of § 135(b) are applicable, proposed claims 104 and 105, which Krieg presented after the Critical Date, are *prima facie* unpatentable to Krieg and Krieg has failed to prove otherwise.

***2. "Desensitizing" Requires The Use of A Particular Allergen***

Proposed claim 104 is silent regarding the administration of antigen in the claimed method of treating asthma, whereas claims 60 and 76 specifically recite "desensitizing a subject against the occurrence an allergic reaction."

Krieg's witnesses (Dr. Center and Dr. Wallner) and Raz's witness (Dr. Schleimer) agree that one of ordinary skill in the art would have understood "desensitizing a subject" to refer to the deliberate and repeated administration of small amounts of a particular allergen for the purpose of altering the subject's immune response against the occurrence of an allergic reaction to the particular antigen. *See*, Facts 210-215. Therefore, one of ordinary skill in the art would have understood that claims 60 and 76 require the administration of antigen, whereas proposed claim 104 is silent regarding the administration of an antigen. *See*, Facts 210-215. Therefore, claims 60 and 76 are materially different in scope and subject matter from proposed claim 104, which Krieg has presented to overcome unpatentability of Krieg's Involved Claims. Assuming

the provisions of § 135(b) are applicable, proposed claim 104, which Krieg presented after the Critical Date, is *prima facie* unpatentable to Krieg and Krieg has failed to prove otherwise.

### *3. Krieg's Reliance on Claim 44 is Misplaced*

On page 17, lines 20-21, Krieg argues that section 135(b)(1) is satisfied since claim 104 does not differ from claim 44 in any material difference. On page 17, lines 18-19, Krieg states that "the scope of claim 104 is the same or substantially the same as the scope of Krieg claim 44."

**Raz's response is** that Krieg's reliance on claim 44 to avoid a finding of unpatentability under § 135(b) is illogical and legally misplaced.

If the Board considers Krieg Motion 4, then the Board will have determined that Krieg claim 44 is unpatentable to Krieg for lack of written description, enablement, and/or patentability over prior art. If, as Krieg asserts, Krieg claims 44 and 104 are commensurate in scope, then Krieg claim 104 is unpatentable to Krieg for essentially the same reason(s) the Board held Krieg claim 44 unpatentable. The issue of whether claim 104 is patentable to Krieg under 35 U.S.C. § 135(b) would be moot in view of the other grounds of unpatentability.

On the other hand, if claim 104 is somehow patentable to Krieg while claim 44 is not, then claim 104 and claim 44 must differ in some material limitation and Krieg cannot rely on the earlier filing date of claim 44 to avoid a finding of unpatentability under 35 U.S.C. § 135(b). *See Regents of the Univ. of California v. Univ. of Iowa Research Found.*, 455 F.3d 1371, 79 U.S.P.Q.2d 1687 (Fed. Cir. 2006)

In summary, Krieg's reliance on claim 44 to avoid a finding of unpatentability under § 135(b) is untenable.

**G. Krieg's New Claims Do Not Interfere with Raz's Claims**

On page 2, line 9, to page 8, line 4, Krieg argues that proposed claims 104 and 105 interfere-in-fact with Raz claim 17.

**Raz's response is** that, as a preliminary matter, an interference-in-fact can exist between proposed claim 104 and Raz claim 17 only if the Board determines that proposed claim 104 is patentable. As explained above, Krieg repeatedly asserts that proposed claim 104 is of the same scope as Krieg claim 44 in terms of treating asthma by administering an immunostimulatory polynucleotide without administering an antigen as part of the treatment. In considering Krieg Motion 4, the Board will have determined that Krieg's involved claims (*e.g.*, claim 44) are unpatentable to Krieg as failing to satisfy the written description and/or enablement requirements of 35 U.S.C. § 112, first paragraph. The same conclusion would be applicable to claims of admittedly identical scope, such as proposed claim 104. If claim 104 is not patentable to Krieg, then it cannot provide the basis for an interference-in-fact.

On page 6, line 5 to page 7, line 1, Krieg argues that proposed claim 104 would have rendered obvious the recitation in Raz claim 17 reciting "wherein the immunostimulatory polynucleotide is administered without the antigen, including without a polynucleotide encoding the antigen." At page 6, lines 18 to page 7, line 1, Krieg argues that, based on the known ability of CG nucleic acids to stimulate "Th1 cytokines" without the presence of antigen, one of ordinary skill in the art would have had a reasonable expectation of success practicing the method of Raz claim 17 in view of Krieg claim 104.

**Raz's response** is that Krieg's assertions are without merit.

At the time of Raz's involved application, allergic asthma was recognized as an antigen-specific disease. As noted on page 10, lines 1-6 of Krieg Motion 4:

> Desensitization therapy was a common approach to treating allergies as at [sic] the filing date of the Raz patent (U.S. Patent No. 6,498,148, Ex. 1001). (Fact 9). Desensitization therapy was also used to treat allergic asthma. (Fact 10). Desensitization therapy involves **repeated administration of allergen** to a subject in order to tolerize the subject to the allergen. (Fact 11). Subjects undergoing desensitization therapy, including asthmatic subjects, **are administered antigen** (or allergen). (Fact 12). [Emphasis added.]

Therefore, by Krieg's own admission, the state of the art at the time of filing Raz's application was such that one of ordinary skill in the art would have known that the treatment of allergic asthma involved the administration of antigen. *See*, Facts 225-226. This understanding would have been reinforced by the teachings of Krieg *et al* in a series of publications spanning 1996 to 1998. *See*, Facts 227-250. Therein, Krieg repeatedly described animal models wherein the immunostimulatory polynucleotide was administered with antigen and wherein the immune responses thereto were antigen-specific. *See*, Facts 227-250. Significantly, Krieg concurrently reported that administration of the immunostimulatory polynucleotide without antigen was ineffective in treating asthmatic indicators. *See*, Facts 227-250.

Indeed, Raz's specification draws a very clear and undisputed line between the desensitization therapies advanced by Krieg and others and the novel methods invented by Dr. Raz. *See*, Fact 224. For example, at column 2, lines 43-50 of his earliest filed application, Dr. Raz stated reported the following:

> Unlike canonical immunotherapy, immunity is stimulated by this method of the invention ***even when no additional antigen is introduced into the host.*** Thus, use of the method to boost the immune responsiveness of a host to subsequent challenge by a sensitizing antigen ***without immunization*** avoids the risk of immunization-induced anaphylaxis, suppresses IgE production in response to the antigen challenge ***and eliminates the need to identify the sensitizing antigen for use in immunization.***" [*See*, Fact 224; Emphasis added].

In summary, there is nothing in Krieg's Proposed Claims, even when combined with the prior art, that would have motivated one of ordinary skill in the art to treat asthma by

administering an immunostimulatory polynucleotide without administration of antigen as part of the treatment. *See*, Facts 227-250. Moreover, as reflected by Krieg's published reports, there would not have been a reasonable expectation of success in administering an immunostimulatory polynucleotide without administering an antigen to treat asthma. *See*, Facts 227-250. Accordingly, neither proposed claim 104 nor proposed claim 105 would have rendered obvious the subject matter of Raz claim 17 (or Raz's proposed new claim 58 to U.S. Application No. 10/229,208 application).

## VI. CONCLUSION

Accordingly, the Board should deny Krieg Motion 4.

Respectfully submitted,

September 10, 2007

/Oliver R. Ashe, Jr./
Oliver R. Ashe, Jr.
Registration No. 40,491
Counsel for Party Raz

**ASHE, P.C.**
11440 Isaac Newton Square North
Suite 210
Reston, VA 20190
Tel.: 703-467-9001
Fax: 703-467-9002
E-mail: oashe@ashepc.com

## Appendix 1

## THE EVIDENCE

### I. Exhibits Cited

The following exhibits are cited in support of this opposition:

| | |
|---|---|
| **Ex. 1050** | Amendment to add claims 104 and 105, filed July 25, 2007, in U.S. Patent Application Serial No. 09/337,584 |
| **Ex. 1051** | Second Declaration of David M. Center, M.D., dated July 25, 2007 |
| **Ex. 1054** | Preliminary Amendment filed June 21, 1999, in U.S. Patent Application Serial No. 09/337,584 |
| **Ex. 2001** | Declaration of Dr. Robert Schleimer |
| **Ex. 2003** | U.S. Patent No. 6,498,148, issued December 24, 2002, to Raz |
| **Ex. 2004** | U.S. Patent Application No. 09/337,584, filed June 21, 1999, to Krieg *et al.* |
| **Ex. 2005** | U.S. Application No. 08/960,774, filed October 30, 1997, to Krieg *et al.* |
| **Ex. 2006** | U.S. Application No. 08/738,652, filed October 30, 1996, to Krieg *et al.* |
| **Ex. 2008** | Kline *et al.*, "CpG Motif Oligonucleotides are Effective in Prevention of Eosinophilic Inflammation in a Murine Model of Asthma," *J. Investig. Med.* 44(7): 380A (September 1996). |
| **Ex. 2009** | Kline *et al.*, "Immune Redirection by CpG Oligonucleotides: Conversion of a Th2 Response to a Th1 Response in a Murine Model of Asthma," *J. Investig. Med.* 45(3): 282A (March 1997). |
| **Ex. 2010** | Kline *et al.*, "Cutting Edge: Modulation of Airway Inflammation by CpG Oligodeoxynucleotides in Murine Model of Asthma" *J. Immunol.* 160: 2555-2559 (January 14, 1998). |
| **Ex. 2016** | Roitt, Ivan *et al.*, *Immunology* pp. 1.6, 19.19 (2d ed. 1989). |
| **Ex. 2017** | Katzung, Bertram G., *Basic & Clinical Pharmacology* pp. 332-335 (9th ed. 2004). |
| **Ex. 2042** | Transcript of the Cross-Examination Deposition of Barbara P. Wallner, Ph.D., taken August 27, 2007. |

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|---|---|
| **Ex. 2043** | Transcript of the Cross-Examination Deposition of David M. Center, M.D., taken August 16, 2007. |
| **Ex. 2046** | Transcript of the Cross-Examination Deposition of Robert P. Schleimer, Ph.D., taken July 31, 2007. |
| **Ex. 2047** | DVD of the Cross-Examination Deposition of Barbara P. Wallner, Ph.D., taken August 27, 2007 (Disc 1 of 3). |
| **Ex. 2048** | DVD of the Cross-Examination Deposition of Barbara P. Wallner, Ph.D., taken August 27, 2007 (Disc 2 of 3). |
| **Ex. 2050** | DVD of the Cross-Examination Deposition of David M. Center, M.D., taken August 16, 2007 (Disc 1 of 2). |
| **Ex. 2052** | Office Action mailed January 13, 2005, in U.S. Patent Application No. 09/337,584. |
| **Ex. 2053** | Amendment mailed April 12, 2005, in U.S. Patent Application No. 09/337,584. |
| **Ex. 2054** | Preliminary Amendment dated December 22, 2003, in U.S. Patent Application No. 10/743,625. |
| **Ex. 2055** | Office Action dated July 6, 2005, in U.S. Patent Application No. 10/743,625. |
| **Ex. 2056** | Office Action dated July 13, 2007, in U.S. Patent Application No. 10/743,625. |

## II. Papers Cited

The following papers are cited in support of this opposition:

| | |
|---|---|
| **Paper No. 1** | Declaration of Interference, filed January 8, 2007 |
| **Paper No. 2** | Standing Order |
| **Paper No. 22** | Redeclaration, filed March 14, 2007 |
| **Paper No. __** | Raz Clean Copy of Claims, filed January 22, 2007 |
| **Paper No. __** | Krieg Clean Copy of Claims, filed January 22, 2007 |
| **Paper No. __** | Raz Motion 1, filed June 18, 2007 |
| **Paper No. __** | Raz Motion 3, filed June 18, 2007 |

**Paper No. __** Krieg Contingent Responsive Motion, filed July 25, 2007

## III. Appendices Cited

The following appendices are cited in support of this opposition:

**Appendix 1** The Evidence

**Appendix 2** Material Facts Alleged In Krieg Contingent Responsive Motion, Followed By Raz's Responses

**Appendix 3** Additional Materials Facts Relied Upon By Raz In Support Of This Opposition

## Appendix 2

## MATERIAL FACTS ALLEGED IN KRIEG CONTINGENT RESPONSIVE MOTION, FOLLOWED BY RAZ'S RESPONSES

1. Count 1 is defined as Krieg claim 44 or Raz claim 17. (Ex. 1005).

**Raz response: Admitted.**

2. Krieg claim 104 recites a subject that is hypersensitized to an allergen that induces an asthmatic response while Raz claim 17 recites a subject sensitized to an asthma-stimulating antigen. (Ex. 1050; Raz Clean Copy of Claims).

**Raz response: Denied.**

3. The terms "hypersensitized" and "sensitized" in the contexts of these teachings intend the same meaning and are therefore interchangeable. (Ex. 1051, ¶ 16).

**Raz response: Denied.**

4. Krieg claim 104 recites an allergen that induces an asthmatic response while Raz claim 17 recites an asthma-stimulating antigen. (Ex. 1050).

**Raz response: Admitted.**

5. The antigen of Raz claim 17 and the allergen of Krieg claim 104 have the same meaning. (Ex. 1051, ¶ 17).

**Raz response: Denied.**

6. Krieg claim 105 recites that allergen is administered to the subject. (Ex. 1050).

**Raz response: Admitted.**

7. The timing of administration of the allergen is not limited, and thus the claim embraces administration of allergen before and after administration of the CG nucleic acid. (Ex. 1051, ¶¶ 25, 26).

**Raz response: Denied.**

8. Krieg claim 105 also embraces administration of the allergen at the same time as the CG nucleic acid (i.e., co-administration). (Ex. 1051, ¶ 26).

**Raz response: Unable to admit or deny.**

9. Desensitization therapy was a common approach to treating allergies as at the filing date of the Raz patent (U.S. Patent No. 6,498,148). (Ex. 1001, front page; Ex. 2001, ¶ 29).

**Raz response: Admitted.**

10. Desensitization therapy was also used to treat allergic asthma. (Ex. 1001, col. 2, lines 20-28).

**Raz response: Admitted-in-part and denied-in-part.**

11. Desensitization therapy involves repeated administration of allergen to a subject in order to tolerize the subject to the allergen. (Ex. 2001, ¶ 30).

**Raz response: Admitted.**

12. Subjects undergoing desensitization therapy, including allergic asthmatic subjects, are administered antigen (or allergen). (Ex. 2001, ¶ 30).

**Raz response: Admitted.**

13. Raz claim 17 and Krieg claim 104 both recite "A method for treating asthma, comprising" in the preamble. (Ex. 1050; Raz Clean Copy of Claims).

**Raz response: Admitted.**

14. Raz claim 17 recites "administering to a mammal sensitized to an asthma-stimulating antigen". (Raz Clean Copy of Claims).

**Raz response: Admitted.**

15. Krieg claim 104 recites "administering to a subject with a hypersensitivity to an

allergen that induces an asthmatic response". (Ex. 1050).

**Raz response: Admitted.**

16. Mammals, as recited in Raz claim 17, are a subgenus of subjects, as recited in Krieg claim 104. (Ex. 1051, ¶ 14).

**Raz response: Unable to admit or deny.**

17. Sensitivity, as recited in Raz claim 17, and hypersensitivity, as recited in Krieg claim 104, within the context of the Raz patent and the Krieg application would be understood by one of ordinary skill in the art to have an equivalent meaning. (Ex. 1051, ¶ 16).

**Raz response: Denied.**

18. An asthma-stimulating antigen, as recited in Raz claim 17, is an allergen that induces an asthmatic response, as recited in Krieg claim 104. (Ex. 1051, ¶ 17).

**Raz response: Admitted.**

19. A mammal sensitized to an asthma-stimulating antigen, as recited in Raz claim 17, is a subgenus of a subject with a hypersensitivity to an allergen that induces an asthmatic response, as recited Krieg claim 104 (Ex. 1051, ¶ 18).

**Raz response: Unable to admit or deny.**

20. Subjects, as recited in Krieg claim 104, include mammals, as recited in Raz claim 17. (Ex. 1001, page 19, lines 27-28; Ex. 1051, ¶ 14).

**Raz response: Admitted.**

21. Asthma afflicts humans. (Ex. 1051, ¶ 15).

**Raz response: Admitted-in-part and denied-in-part.**

22. Humans are mammals. (Ex. 1003, ¶ 15; Ex. 1051, ¶ 15).

**Raz response: Admitted.**

23. Hypersensitivity is equivalent to sensitivity. (Ex. 1051, ¶ 16).

**Raz response: Denied.**

24. Hypersensitized subjects, as recited in Krieg claim 104, include sensitized mammals, as recited in Raz claim 17. (Ex. 1051, ¶ 18).

**Raz response: Denied.**

25. An allergen that induces an asthmatic response, as recited in Krieg claim 104, is an asthma-stimulating antigen, as recited in Raz claim 17 (Ex. 1051, ¶ 17).

**Raz response: Admitted.**

26. Raz claim 17 recites "an immunostimulatory polynucleotide comprising an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5'-cytosineguanine-3', wherein the ISS is at least 6 nucleotides in length". (Raz Clean Copy of the Claims).

**Raz response: Admitted-in-part and denied-in-part.**

27. Krieg claim 104 recites "an immunostimulatory nucleic acid, having a sequence including at least the following formula: 5' X1 X2 CG X3 X4 3' wherein C is unmethylated, wherein X1X 2 and X3X4 are nucleotides". (Ex. 1050).

**Raz response: Admitted.**

28. Raz claim 17 recites a genus of nucleic acids having CG dinucleotides in which the C nucleotide may be methylated or unmethylated. (Raz Clean Copy of the Claims).

**Raz response: Denied.**

29. Krieg claim 104 recites a subgenus of nucleic acids having CG dinucleotides in which the C nucleotide is unmethylated. (Ex. 1050).

**Raz response: Admitted-in-part and denied-in-part.**

30. At the time of filing of the Raz patent, it was well known in the art that

unmethylated C nucleotides in CG dinucleotides were important for immunostimulation. (Ex. 1001, front page; Ex. 1018, page 546, col. 1, line 24 through to col. 2, line 8; col. 2, lines 14-23; Ex. 1045, col. 10, lines 13-22).

**Raz response: Admitted.**

31. The prior art teaches that the immunostimulatory activity of nucleic acids comprising a CG dinucleotide depends on the C being unmethylated. (Ex. 1018, page 546, col. 1, line 24 through to col. 2, line 8; col. 2, lines 14-23; Ex. 1045, col. 10, lines 13-22).

**Raz response: Unable to admit or deny.**

32. The Raz patent also states that "ISS-ODN ... may include at least one unmethylated CpG". (Ex. 1001, col. 8, lines 31-33).

**Raz response: Admitted.**

33. Raz claim 17 recites a polynucleotide having at least 6 nucleotides and comprising a CG dinucleotide. (Raz Clean Copy of the Claims).

**Raz response: Admitted-in-part and denied-in-part.**

34. Krieg claim 104 recites a hexamer (i.e., 6-mer) sequence in which a CG dinucleotide is flanked on both sides by two nucleotides. (Ex. 1050).

**Raz response: Admitted-in-part and denied-in-part.**

35. This limitation in Raz claim 17 is slightly broader than that in Krieg claim 104 because the location of the CG dinucleotide within the hexamer sequence is restricted in Krieg claim 104 while in Raz claim 17 it is not. (Ex. 1051, ¶ 20).

**Raz response: Unable to admit or deny.**

36. The prior art teaches either a similar formula to that recited in Krieg claim 104 or exemplary oligonucleotides that are embraced by this formula. (Ex. 1018, Table 1,

oligonucleotides 1, 1c, 1d, 2, 3D, 3Da, 3Db; Ex. 1045, col. 8, lines 3-23).

**Raz response: Unable to admit or deny.**

37. Raz claim 17 recites "wherein the immunostimulatory polynucleotide does not comprise a nucleotide sequence encoding the antigen". (Raz Clean Copy of the Claims).

**Raz response: Admitted-in-part and denied-in-part.**

38. Krieg claim 104 is silent with respect to whether the CG nucleic acid encodes an antigen. (Ex. 1050).

**Raz response: Admitted.**

39. The prior art teaches that immunostimulation by CG nucleic acids is independent of whether the nucleic acids code for any antigen (or other protein), as evidenced by CG nucleic acids that do not code for any antigen (or other protein). (Ex. 1018, Table 1; Ex. 1045, Table 1).

**Raz response: Unable to admit or deny.**

40. Most if not all of the CG nucleic acids that are 8-100 nucleotides in length will not encode an antigen or other protein. (Ex. 1051, ¶ 21).

**Raz response: Unable to admit or deny.**

41. In order to encode antigens or other proteins, these nucleic acids would require transcriptional and translational regulatory elements in addition to the antigen coding sequence itself. (Ex. 1051, ¶ 21).

**Raz response: Denied.**

42. For example, nucleic acids at the lower end of this range (e.g., 8-mers) would not be long enough to comprise both regulatory and coding sequences. (Ex. 1051, ¶ 21).

**Raz response: Unable to admit or deny.**

43. These nucleic acids would not encode an antigen. (Ex. 1051, ¶ 21).

**Raz response: Unable to admit or deny.**

44. Raz claim 17 recites "wherein the immunostimulatory polynucleotide is administered without the antigen, including without a polynucleotide encoding the antigen". (Raz Clean Copy of Claims).

**Raz response: Admitted-in-part and denied-in-part.**

45. Krieg claim 104 is silent with respect to whether an antigen is administered. (Ex. 1050).

**Raz response: Admitted.**

46. Krieg claim 104 therefore embraces administering the nucleic acid with or without an antigen. (Ex. 1050).

**Raz response: Admitted.**

47. At the time of filing of the Raz patent, CG nucleic acids when administered without antigen had been shown to stimulate or modulate immune responses, induce particular cytokine profiles, and treat various conditions. (Ex. 1001, front page; Ex. 1018, page 547, col. 1, lines 8-13, and Table 1; Ex. 1045, col. 6, lines 2-6 and 28-47; col. 19, lines 4-9; Table 1; col. 14, lines 42-46).

**Raz response: Unable to admit or deny.**

48. The ability of CG nucleic acids to stimulate Th1 cytokines thereby causing a Th2 to Th1 shift independent of antigen is disclosed in U.S. Patent 6,207,646, the grandparent of the instant application. (Ex. 1044, col. 6, lines 10-15 and 59-65; col. 8, lines 6-9; col. 9, lines 19-33; col. 34, lines 9-12, 18-29, 33-45; col. 35, lines 9-12; and col. 42, line 66 through to col. 43, line 2).

**Raz response: Denied. Furthermore, Fact 48 is hearsay. See Fed. R. Evid. 801 and**

**802 and SO ¶ 152.2.1.**

49. One of ordinary skill in the art would have been motivated to administer a CG nucleic acid without antigen in view of the knowledge in the art that antigen administration was unnecessary for obtaining the desired immune effects, including induction of the desired cytokine profiles. (Ex. 1051, ¶ 22).

**Raz response: Denied.**

50. The person of ordinary skill would have also had a reasonable expectation of success in doing so for the same reasons. (Ex. 1051, ¶ 22).

**Raz response: Denied.**

51. Raz claim 17 and Krieg claim 104 both recite "an effective amount for treating asthma in the subject". (Raz Clean Copy of Claims; Ex. 1050).

**Raz response: Denied.**

52. Raz claim 17 recites "wherein the ISS is at least six nucleotides in length". (Raz Clean Copy of Claims).

**Raz response: Admitted-in-part and denied-in-part.**

53. Krieg claim 104 recites "wherein the nucleic acid has a length of 8 to 100 nucleotides". (Ex. 1050).

**Raz response: Denied.**

54. Raz claim 17 recites a genus of nucleic acids that are at least 6 nucleotides in length. (Raz Clean Copy of Claims; Ex. 1051, ¶ 24).

**Raz response: Denied.**

55. Krieg claim 104 recites a subgenus of nucleic acids that are 8-100 nucleotides in length. (Ex. 1050; Ex. 1051, ¶ 24).

**Raz response: Denied.**

56. The prior art teaches that CG nucleic acids within the 8-100 nucleotide size range are immunostimulatory. (Ex. 1018, Table 1; Ex. 1044, col. 6, lines 37-40; col. 11, lines 29-41; Ex. 1045, col. 6, lines 8-20; col. 10, lines 36-38).

**Raz response: Admitted-in-part and denied-in-part.**

57. Krieg claim 105 recites "further comprising administering the allergen". (Ex. 1050).

**Raz response: Admitted-in-part and denied-in-part.**

58. Raz claim 17 recites "wherein the immunostimulatory polynucleotide is administered without the antigen, including without a polynucleotide encoding the antigen". (Raz Clean Copy of Claims).

**Raz response: Admitted-in-part and denied-in-part.**

59. The timing of allergen administration in Krieg claim 105 is not limited (i.e., it can be before, during and/or after administration of the nucleic acid). (Ex. 1051, ¶ 25).

**Raz response: Denied.**

60. Giving Raz claim 17 its broadest reasonable interpretation, it excludes only coadministration of the antigen and the polynucleotide, and not antigen administration prior to or after the polynucleotide. (Ex. 1051, ¶ 27).

**Raz response: Denied.**

61. The prior art teaches use of densensitization therapy (i.e., repeated administration of antigen or allergen) to treat allergy, including allergic asthma. (Ex. 1001, col. 2, lines 20-28; Ex. 2001, ¶ 29).

**Raz response: Admitted-in-part and denied-in-part.**

62. Krieg claim 105 embraces at least administration of the allergen prior to and/or after nucleic acid administration. (Ex. 1051, ¶ 25).

**Raz response: Denied.**

63. Raz's contingent claim is as follows:

> A method for treating asthma, comprising: administering to a mammal sensitized to an asthma-stimulating antigen an immunostimulatory polynucleotide comprising an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5'-cytosine-guanine-3', wherein the immunostimulatory polynucleotide has a length of 6 to 200 nucleotides, wherein the immunostimulatory polynucleotide does not comprise a nucleotide sequence encoding the antigen, and wherein the immunostimulatory polynucleotide is administered without the antigen, including without a polynucleotide encoding the antigen, and in an amount sufficient to treat asthma. (Paper No. 73).

**Raz response: Admitted.**

64. The new Raz claim is identical to Raz claim 17, except that it requires that the polynucleotide have a length of 6 to 200 nucleotides. (Ex. 1051, ¶ 30).

**Raz response: Admitted.**

65. The prior art teaches that CG nucleic acids having a length of 8-100 nucleotides are immunostimulatory. (Ex. 1018, Table 1; Ex. 1045, col. 6, lines 8-20; col. 10, lines 36-38).

**Raz response: Admitted-in-part and denied-in-part.**

66. Krieg claim 104 recites a subgenus of nucleic acids that are 8-100 nucleotides in length (Ex. 1050; Ex. 1051,¶ 31).

**Raz response: Unable to admit or deny.**

67. Raz claim recites a genus of nucleic acids that are 6-200 nucleotides in length. (Ex. 1051,¶ 31).

**Raz response: Unable to admit or deny.**

68. Krieg claims 104 and 105 recite a method of treating asthma by administering a

CG nucleic acid to a subject hypersensitized to an allergen that induces an asthmatic response. (Ex. 1050).

**Raz response: Admitted-in-part and denied-in-part.**

69. Krieg claim 105 further recites that an allergen is administered to the subject. (Ex. 1050).

**Raz response: Admitted-in-part and denied-in-part.**

70. The Krieg application describes a class of nucleic acids having a common structural motif (i.e., a CG dinucleotide) that when administered to a subject results in an altered immune response. (Ex. 1002, page 7 line 31 through to page 8, line 2; page 8, lines 20-28; page 9, lines 8-12; page 16, lines 23-25 and 27-29).

**Raz response: Admitted-in-part and denied-in-part.**

71. The data in the Krieg application, including those presented in Tables 1-3, establish that CG nucleic acids are immunostimulatory. (Ex. 1002, Tables 1B, 1C, 2 and 3).

**Raz response: Denied. Furthermore, Fact 71 is hearsay. See Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

72. The ability of CG nucleic acids to induce a Th1 immune response are described throughout the Krieg application. (Ex. 1002, page 8, lines 22-23 and 25-27; page 9, lines 8-9; page 53, line 26 through to page 54, line 5).

**Raz response: Denied.**

73. The Krieg application includes many examples relating to the induction of, for example, IL-6, IL-12 and IFN-gamma, all of which are Th1 cytokines. (Ex. 1002, Figs. 1B, 1C, 2, 3, 14, 15, and Tables 2, 3, 4; Ex. 1051, ¶ 32).

**Raz response: Denied.**

74. The data presented in Tables 5 and 13 demonstrate that CG nucleic acid stimulate a Th1 response profile in human cells also. (Ex. 1002, page 8, lines 22-23 and 25-27; page 9, lines 8-9; page 53, line 26 through to page 54, line 5).

**Raz response: Denied. Furthermore, Fact 74 is hearsay. *See* Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

75. CG nucleic acids also affect Th2 immune responses by virtue of their Th1 induction properties. (Ex. 1002, page 7 line 31 through to page 8, line 2; page 8, lines 20-23; page 9, lines 8-12; page 53, lines 19-23 and 26-31; page 54, lines 4-5 and 26-27).

**Raz response: Denied. Furthermore, Fact 75 is hearsay. *See* Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

76. Raz's expert Dr. Schleimer acknowledges that "in general, Th1 cells and Th2 cells exert a negative influence on one another, such that they are reciprocally regulated" and that "secretion of Th1 cytokines inhibits secretion of Th2 cytokines and vice versa". (Ex. 2001, ¶ 24).

**Raz response: Admitted.**

77. One of ordinary skill in the art would conclude that CG nucleic acids would have a "negative influence" on a Th2 immune response by virtue of their Th1 induction profile. (Fact 77, Ex. 1051, ¶ 34).

**Raz response: Denied.**

78. The Krieg application teaches that CG nucleic acids are able to effect a Th2 to Th1 shift. (Ex. 1002, page 7 line 31 through to page 8, line 2; page 8, lines 20-23; page 9, lines 8-12; page 53, lines 19-23 and 26-31; page 54, lines 4-5 and 26-27).

**Raz response: Denied.**

79. The Krieg application teaches that CG nucleic acids can be used to treat asthma

by virtue of their ability to induce a Th2 to Th1 shift. (Ex. 1002, page 9, lines 8-13; page 17, lines 14-16; page 53, line 26 through to page 54, line 5; page 54, lines 26-28).

**Raz response: Denied.**

80. The immune system in an allergic asthmatic subject has cytokine activity that is skewed toward a Th2 response. (Fact 80, Ex. 1051, ¶ 37).

**Raz response: Admitted.**

81. This is acknowledged by Raz. (Ex. 2001, ¶ 32).

**Raz response: Unable to admit or deny.**

82. Raz's expert, Dr. Schleimer, states that "one of ordinary skill in the art would have understood that there are significant therapeutic implications stemming from any ability to shift a Th2 response to a Th1 response" and that "In particular, a shift in a Th2 response to a Th1 response reduces or suppresses allergic inflammation". (Ex. 2001, ¶ 25).

**Raz response: Admitted.**

83. In view of the teaching in the Krieg application and the knowledge in the art at the time, one of ordinary skill in the art would have concluded that CG nucleic acids would be useful in the treatment of asthma. (Ex. 1051, ¶ 36).

**Raz response: Unable to Admit or Deny.**

84. Accordingly, no undue experimentation would be required to practice the method of Krieg claim 104. (Ex. 1051, ¶ 39).

**Raz response: Unable to admit or deny.**

85. The Krieg application teaches Th1 induction by CG nucleic acids on murine and human cells either in vitro or in vivo. (Ex. 1002, Figs. 1B, 1C, 3, and Tables 2, 3, 4, 5, 13).

**Raz response: Denied.**

86. Tables 1-3 demonstrate that CG nucleic acids are capable of activating murine B cells and inducing cytokine expression in murine cells in vitro. (Ex. 1002, page 22, Table 1; page 23, Table 2; page 26, Table 3).

**Raz response: Denied. Furthermore, Fact 86 is hearsay. *See* Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

87. Table 5 presents data from an experiment in which CG nucleic acids were tested for their ability to induce cytokine expression in human cells. (Ex. 1002, page 30, Table 5).

**Raz response: Admitted.**

88. These data demonstrate that CG nucleic acids are capable of inducing cytokine expression in vitro. (Ex. 1051, ¶ 33).

**Raz response: Unable to admit or deny. Furthermore, Fact 88 is hearsay. *See* Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

89. The data obtained in the in vivo experiments such as those shown in Table 4 and Example 12 are consistent with the data obtained in the in vitro experiments, confirming that the pattern of cytokine release and Th1 effects can be induced in vivo by the claimed CG nucleic acids. (Ex. 1002, page 28, Table 4; page 28, line 14 through to page 29, line 31; Figs. 14 and 15).

**Raz response: Denied. Furthermore, Fact 89 is hearsay. *See* Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

90. The Krieg application further demonstrates that CG nucleic acids induce their Th1 effects independent of antigen administration. (Ex. 1002, Figs. 1B, 1C, 2, 3, and Tables 1, 2, 3, 4, 5, 13).

**Raz response: Denied.**

91. In vivo experiments in mice show that CG nucleic acids induce a Th1 cytokine

profile even when administered without antigen or allergen. (Ex. 1002, page 28, line 14 through to page 29, line 31).

**Raz response: Unable to Admit or Deny. Furthermore, Fact 91 is hearsay. *See* Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

92. CG nucleic acids therefore induce a Th1 immune profile in vivo even when antigen is not administered to a subject. (Ex. 1002, page 52, line 29 through to page 53, line 3; page 53, lines 19-31).

**Raz response: Unable to Admit or Deny.**

93. Example 12 confirms that a CG nucleic acid would have the ability to initiate in vivo, even in the presence of an antigen, a pattern of cytokine release which would drive the immune system toward a Th1 response and would treat asthma. (Ex. 1002, page 53, line 32 through to page 54, line 5).

**Raz response: Denied. Furthermore, Fact 93 is hearsay. *See* Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

94. Example 12 also confirms that CG nucleic acids not only shift the cytokine response, but are effective in influencing other important therapeutic aspects of asthma, such as infiltration of cells and fluid into the lungs. (Ex. 1002, pge 54, lines 1-5).

**Raz response: Denied. Furthermore, Fact 94 is hearsay. *See* Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

95. Figures 9 and 10 show that the CG nucleic acid maintained cell count in response to an allergen at a level close to that of the saline control, whereas in the absence of CG nucleic acid cell counts increased dramatically. (Ex. 1002, Figs. 9 and 10).

**Raz response: Unable to admit or deny. Furthermore, Fact 95 is hearsay. *See* Fed.**

**R. Evid. 801 and 802 and SO ¶ 152.2.1.**

96. Figure 11 shows that the CG nucleic acid resulted in an eosinophil count similar to that of the saline control, whereas the non-CG nucleic acid (control oligo) resulted in an eosinophil count similar to that induced by the allergen alone. (Ex. 1002, Fig. 11).

**Raz response: Unable to Admit or Deny. Furthermore, Fact 74 is hearsay.** ***See*** **Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

97. Figure 12 shows that the ability of CG nucleic acids to suppress eosinophil infiltration is dose dependent. (Ex. 1002, Fig. 12).

**Raz response: Denied. Furthermore, Fact 97 is hearsay.** ***See*** **Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

98. Figure 13 shows that the resultant inflammatory response from allergen exposure correlates with the levels of the Th2 cytokine IL-4 in the lung and that the CG nucleic acid maintains suppression of IL-4 expression. (Ex. 1002, Fig. 13).

**Raz response: Denied. Furthermore, Fact 98 is hearsay.** ***See*** **Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

99. Figures 14 and 15 show that administration of the CG nucleic acid can redirect the cytokine response of the lung to production of IL-12 and IFN-g, indicating the Th1 type of immune response. (Ex. 1002, Figs. 14 and 15).

**Raz response: Denied. Furthermore, Fact 99 is hearsay.** ***See*** **Fed. R. Evid. 801 and 802 and SO ¶ 152.2.1.**

100. Based upon these teachings, one of ordinary skill in the art would have concluded that CG nucleic acids would bias the immune system toward Th1, even when administered with an antigen that otherwise would provoke a Th2 response. (Ex. 1051, ¶ 38).

**Raz response: Denied.**

101. The prior art taught the ability to treat allergic asthma by modulating the Th2 to Th1 balance independent of antigen (or allergen) administration. (Ex. 1009, abstract; Ex. 1010, abstract and claims; Ex. 1052, abstract, claims 1-3).

**Raz response: Denied.**

102. Li et al., J. Immunol., 1996; 157:3216-9 and US 6,121,247 describe a method for treating allergic asthma using Th1 cytokine IFN-gamma gene therapy, independent of antigen (or allergen) administration. (Ex. 1009, abstract; Ex. 1010, abstract and claims).

**Raz response: Admitted-in-part and denied-in-part.**

103. US 5,767,097 claims a method for treating subjects having allergy or allergic asthma by promoting a Th1 response and suppressing a Th2 response, independent of antigen (or allergen) administration. (Ex. 1052, abstract, claims 1-3).

**Raz response: Denied.**

104. The state of the art as of 1996 was such that Th2 to Th1 shifts were known for the treatment of allergic asthma independent of antigen (or allergen) administration. (Ex. 1009, abstract; Ex. 1010, abstract and claims; Ex. 1052, abstract, claims 1-3).

**Raz response: Denied.**

105. The Krieg application provides sufficient guidance for the person of ordinary skill to practice the method of claim 104. (Ex. 1002, page 13, lines 5-25; page 16, line 25 through to page 17, line 17; page 18, line 24 through to page 19, line 26; page 30, line 24 through to page 31, line 5; page 51, line 1 through to page 52, line 1; page 54, line 6 through to page 55, line 1; Tables 1-3 and 5; Ex. 1051, ¶ 39).

**Raz response: Denied.**

106. The Krieg application teaches how to make and administer the CG nucleic acids, and provides many examples of CG nucleic acids and allergens. (Ex. 1002, page 13, lines 5-25; page 16, line 25 through to page 17, line 17; page 18, line 24 through to page 19, line 26; page 30, line 24 through to page 31, line 5; page 51, line 1 through to page 52, line 1; page 54, line 6 through to page 55, line 1; Tables 1-3 and 5).

**Raz response: Unable to Admit or Deny.**

107. Based on this guidance and the knowledge and level of predictability in the art, one of ordinary skill in the art would have been able to practice the methods of Krieg claims 104 and 105 without undue experimentation. (Ex. 1051, ¶ 39).

**Raz response: Unable to Admit or Deny.**

108. The Krieg application is a divisional application of Krieg patent application serial no. 08/960,774. (Ex. 1002, page 1, lines 4-9).

**Raz response: Admitted insofar as "the Krieg application" is the involved USSN 09/337,584, otherwise denied.**

109. As a result, the specification of the Krieg application and the specification of Krieg patent application serial no. 08/960,774 are identical. (Ex. 1002 and Ex. 1053).

**Raz response: Admitted-in-part and denied-in-part.**

110. The Krieg application is a continuation-in-part of Krieg patent application serial no. 08/738,652. (Ex. 1002, page 1, lines 4-9).

**Raz response: Admitted insofar as "the Krieg application" is the involved USSN 09/337,584, otherwise denied.**

111. Krieg patent application serial no. 08/738,652 also fully supports Krieg claims 104 and 105. (Ex. 1053, Figs. 1B, 1C, 2, 3, 6, col. 6, lines 11-15, 30-33, 38-40 and 59-65; col. 7,

lines 36-40; col. 8, lines 6-9; col 9, lines 19-33; col. 10, lines 5-14; col. 11, lines 10-16 and 29-41; col. 12, lines 1-3; col. 13, lines 27-29; col. 14, lines 30-37 and 56-57; col. 19, lines 57-65; col. 20, Table 3, lines 41-42 and line 66 through to col. 21, line 3; col. 21, lines 19-29 and Table 4; col. 22, lines 5-6, 8-11, 19-39 and 47-51, and Table 5; col. 23, Table 5 (cont'd), and lines 38-47; col. 24, lines 65-67; col. 25, Table 7; col. 27, lines 3-4 and 7-9, and Table 8; col. 28, lines 8-11, 19-22, 54 and 61-63, and Table 9; col. 33, lines 22-28 and 49-59; cold. 34, lines 9-12, 18-29 and 33-45; col. 35, lines 9-12; col. 42, lines 37-41 and 66 through to col. 43, line 2).

**Raz response: Denied.**

112. If this motion is granted, Krieg claims 104 and 105 will be added more than one year after the issuance of the Raz patent. (Ex. 1001, front page).

**Raz response: Admitted.**

113. However, claims of the same or substantially the same scope as Krieg claims 104 and 105 were pending in the Krieg application prior to the critical date. (Ex. 1001, front page; Ex. 1054, claims 60 and 76).

**Raz response: Denied.**

114. In particular, at the time of filing of the Krieg application (i.e., June 21, 1999), a preliminary amendment was filed to introduce a number of new claims including claims 60 and 76. (Ex. 1054, claims 60 and 76).

**Raz response: Admitted.**

115. Claim 60 recites a method for desensitizing a subject against the occurrence of an allergic reaction in response to contact with an allergen by administering to the subject an effective amount of a CG nucleic acid having a 5' X1 X2 CG X3 X4 3' motif. (Ex. 1054, claim 60).

**Raz response: Denied.**

116. The allergic reaction of claim 60 may be due to bronchial asthma. (Ex. 1054, claim 62).

**Raz response: Unable to Admit or Deny.**

117. Claim 104 relates to treatment of an allergic asthmatic subject by administering a CG nucleic acid having the same motif. (Ex. 1050).

**Raz response: Denied.**

118. Claim 76 depends from claim 60 and recites that allergen is administered to the subject. (Ex. 1054, claim 76).

**Raz response: Admitted.**

119. Claim 105 recites adminsitration of allergen to the allergic asthmatic subject. (Ex. 1050).

**Raz response: Admitted-in-part and denied-in-part.**

120. Krieg claim 44 recites a method of treating asthma by administering a CG nucleic acid of a particular formula to asthmatic subjects. (Krieg Clean Copy of Claims).

**Raz response: Denied.**

121. Krieg claim 104 recites a method of treating asthma by administering a CG nucleic acid of a particular formula to subjects hypersensitized to an allergen that induces an allergic response. (Ex. 1050).

**Raz response: Denied.**

122. The subjects of Krieg claim 104 are asthmatic subjects that have allergic asthma. (Ex. 1050).

**Raz response: Denied.**

123. Allergic asthma is the most common type of asthma. (Ex. 2001, ¶ 34).

**Raz response: Admitted.**

124. It is clear from the Krieg application that Krieg claims 44 and 104 both rely on the induction of a Th1 response and a Th2 to Th1 immune response shift in order to treat asthma. (Ex. 1051, ¶ 11).

**Raz response: Denied.**

125. The remaining limitations of Krieg claims 44 and 104 are identical. (Ex. 1051, ¶ 12).

**Raz response: Unable to Admit or Deny.**

## Appendix 3

## ADDITIONAL MATERIAL FACTS RELIED UPON BY RAZ IN SUPPORT OF THIS OPPOSITION

### A. The Present Interference

126. The present Interference, Interference No. 105,526, was declared on a single Count, which reads as follows: "A method for treating asthma according to Claim 17 of U.S. Patent 6,498,148 or claim 44 of U.S. Application 09/337,584." (Paper No. 1, p. 4).

127. Raz Claim 17 reads as follows:

> A method for treating asthma, comprising: administering to a mammal sensitized to an asthma-stimulating antigen
>
> an immunostimulatory polynucleotide comprising
>
> an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5'-cytosine-guanine-3',
>
> wherein the immunostimulatory polynucleotide does not comprise a nucleotide sequence encoding the antigen, and wherein the immunostimulatory polynucleotide is administered without the antigen, including without a polynucleotide encoding the antigen, and in an amount sufficient to treat asthma,
>
> wherein the ISS is at least six nucleotides in length. [Raz Clean Copy of Claims, filed January 22, 2007, p. A-1, lns. 2-8, and p. A-2, ln. 17].

128. Krieg claim 44 of Krieg's U.S. Patent Application No. 09/337,584 ("the Krieg Specification") reads as follows:

> A method for treating asthma in a subject, comprising administering to an asthmatic subject an effective amount for treating asthma in the subject of an immunostimulatory nucleic acid, having a sequence including at least the following formula:
>
> $$5'X_1X_2CGX_3X_4\,3'$$
>
> wherein C is unmethylated, wherein $X_1X_2$ and $X_3X_4$ are nucleotides, wherein the nucleic acid has a length of 8 to 100 nucleotides. [Krieg Clean Copy of Claims, filed January 22, 2007, p. 2, lns. 12-17].

129. In the Krieg Contingent Responsive Motion, Krieg moves to add new claims 104 and 105 to U.S. Patent Application No. 09/337,584. (Krieg Contingent Responsive Motion, filed July 25, 2007, p. 1, lns. 2-3).

130. Krieg has proposed new claims 104 and 105 for the purpose of overcoming Raz's unpatentability assertions in Raz Motion 1 and 3. (Krieg Contingent Responsive Motion, filed July 25, 2007, p. 1, 1st ¶).

131. Raz Motion 1 argued that Krieg's involved claims are so broad that they encompass methods of treating asthma by administering an immunostimulatory polynucleotide sequence without administering an antigen as part of the treatment. (Raz Motion 1, filed June 18, 2007, "Overview", pp. 2-3).

132. Raz Motion 1 argued that one of ordinary skill in the art reading Krieg's involved specification would not have considered Krieg to have described or enabled the full scope of a method of treating asthma as recited in Krieg's involved claims. (Raz Motion 1, filed June 18, 2007, "Overview", pp. 2-3).

133. Krieg claim 104 generally recites a method of treating asthma by administration of an ISS. (Ex. 1050, p. 6).

134. Krieg claim 104 does not recite whether the claimed method requires the administration of an ISS without an antigen or a polynucleotide encoding an antigen. (Ex. 1050, p. 6).

135. Krieg's newly presented claims 104 and 105 encompass a method of treating asthma comprising co-administration of an ISS and an antigen. (Ex. 1050, p. 6).

136. Krieg's newly presented claim 104 encompasses a method of treating asthma comprising administering an ISS without co-administration of an antigen. (Ex. 1050, p. 6).

137. Krieg claim 105 explicitly recites administering an allergen. (Ex. 1050, p. 6).

**B. Prosecution of Krieg's Applications**

138. In an Office Action dated January 13, 2005, in the involved '584 application, the Action stated that:

> The method of Example 12 teaches that CpG and the SEA were administered to the asthmatic subject at the same time. It is not clear from the example shown if the CpG administered **alone** to an asthmatic will redirect the cytokine responses and therefore Th1 type immune responses. The pending claims only recite that CpG is administered. [Ex. 2052, p. 5, 1st full ¶; Emphasis added].

139. In an Amendment dated April 12, 2005, in the involved '584 application, Krieg et al stated the following:

> In Example 12, it is necessary to administer the schistosome eggs to the animal to create the airway inflammation characteristic of asthma. In this particular experiment the CpG is given at the same time as the allergen. It may be administered at different times as well. Nothing in Example 12 suggests that the use of CpG oligonucleotides alone as therapy for asthma does not work. [Ex. 2053, p. 12, 3rd full ¶].

140. U.S. Patent Application No. 10/743,625 ("the '625 application") application was filed on December 22, 2003, by Krieg *et al.* (Ex. 2054, p. 1).

141. The Krieg involved '584 application does not contain a claim of benefit to the '625 application. (Ex. 2004; Paper No. 1, p. 5; Paper No. 22, p. 3, lns. 3-8).

142. Krieg substantially copied claims 1-19 of the involved Raz '148 patent in the '625 application. (Ex. 2054).

143. In an office action dated July 6, 2005, in the '625 application, the Examiner rejected claims 19-39. (Ex. 2055, p. 1, "Disposition of Claims").

144. In an office action dated July 13, 2007, in the '625 application, the Examiner rejected claims 19-39. (Ex. 2056, p. 1, "Disposition of Claims").

### C. Krieg's Proposed Claim 104 Fails to Overcome Raz's Arguments With Respect To The Written Description And Enablement Requirements § 112

#### *1. Example 12 of the Krieg Application*

145. The Krieg Specification contains 13 Examples. (Ex. 2004, pp. 55-65).

146. Example 12 of the Krieg Specification relates to a murine model of asthma. (Ex. 2004, pp. 63-65). (Ex. 2001, ¶ 123; Ex. 2004, p. 63, ln. 31 to p. 64, ln. 1).

147. Example 12 of the Krieg Specification describes the co-administration of an ISS and an antigen (*Schistosome* eggs) to one or more mice during the sensitization phase. (Ex. 2001, ¶¶ 124-128; Ex. 2004, p. 11, lns. 27-32; p. 64, lns. 2-11 and lns. 17-21; pp. 63-65; and Fig. 9; Ex. 2042, p. 62, ln. 14 to p. 63, ln. 20; Ex. 2047, Title 1, Ch. 7).

148. Example 12 of the Krieg Specification does not administer an ISS after the sensitization phase or when the mice are challenged with antigen. (Ex. 2004, pp. 63-65; Ex. 2042, p. 62, ln. 14 to p. 63, ln. 20; Ex. 2047, Title 1, Ch. 7).

149. Not used.

150. Example 12 of the Krieg Specification does not describe administration of an ISS to mice without co-administration of an antigen during the sensitization phase. (Ex. 2001, ¶¶ 129-130; Ex. 2004, pp. 63-65; Ex. 2042, p. 62, ln. 14 to p. 63, ln. 20; Ex. 2047, Title 1, Ch. 7).

151. Example 12 of the Krieg Specification reports that mice that had been exposed to *Schistosome* eggs (antigen) without co-administration of ISS during the sensitization phase developed an acute inflammatory response in the lungs after airway challenge with SEA. (Ex.

2001, ¶¶ 124-128; Ex. 2004, p. 11, lns. 27-32; p. 64, lns. 2-11, lns. 17-21, and lns. 25-28; and Fig. 9).

152. Example 12 of the Krieg Specification reports that co-administration of eggs (antigen) and ISS during the sensitization phase almost completely abolished the increase in eosinophils in the lungs after airway challenge with SEA. The Krieg Specification states that eosinophils are the type of inflammatory cell most closely associated with asthma. (Ex. 2001, ¶¶ 124-128; Ex. 2004, p. 11, lns. 27-32; p. 64, lns. 2-11, lns. 17-21, and lns. 28-30; and Fig. 9).

153. Example 12 of the Krieg Specification does not report any data relating to an immunological response to an airway challenge with SEA wherein an ISS was previously administered to mice without co-administration of an antigen. (Ex. 2001, ¶¶ 129-130; Ex. 2004, pp. 63-65).

154. Not used.

155. One of ordinary skill in the art would not have considered Example 12 of the Krieg Specification to convey a method of treating asthma comprising administration of an ISS without co-administration of an antigen. (Ex. 2001, ¶¶ 129-130; Ex. 2004, pp. 63-65).

156. On page 9, at lines 8-12, of the Krieg Specification, Krieg states:

> Furthermore, by redirecting a subject's immune response from Th2 to Th1, the claimed nucleic acid sequences can be used to treat or prevent an asthmatic disorder. In addition, the claimed nucleic acid molecules can be administered to a subject in conjunction with a particular allergen as a type of desensitization therapy to treat or prevent the occurrence of an allergic reaction associated with an asthmatic disorder. [Ex. 2004, p. 9, lns. 8-12].

157. One of ordinary skill in the art would have understood the first sentence of the passage in Fact 156 to disclose the general concept of administering an ISS to treat or prevent an asthmatic disorder, such as allergic or non-allergic asthma. One of ordinary skill in the art would

have understood the first sentence of the passage in Fact 156 to convey a recognition that allergic disorders were considered to be associated with Th2 responses and that ISS compounds were known to redirect an immune response from a Th2 to a Th1 response. (Ex. 2001, ¶ 120).

158. One of ordinary skill in the art would not have considered the first sentence of the passage in Fact 156 to describe any specific method of administering ISS to treat or prevent asthma. (Ex. 2001, ¶ 120).

159. One of ordinary skill in the art would have understood the second sentence of the passage in Fact 156 as additionally noting that, in the context of allergic asthma, the co-administration of an ISS with an asthma-stimulating antigen could be used to desensitize a subject to treat or prevent the occurrence of an allergic reaction associated with an asthmatic disorder. (Ex. 2001, ¶ 121).

160. Page 53, lines 18-25, of the Krieg Specification provides the following disclosure:

> In general, it appears that allergic diseases are mediated by Th2 type immune responses and autoimmune diseases by Th1 immune response. Based on the ability of the immunostimulatory nucleic acid molecules to shift the immune response in a subject from a Th2 (which is associated with production of IgE antibodies and allergy) to a Th1 response (which is protective against allergic reactions), an effective dose of an immunostimulatory nucleic acid (or a vector containing a nucleic acid) alone or in conjunction with an allergen can be administered to a subject to treat or prevent an allergy. [Ex. 2004, p. 53, lns. 18-25; Emphasis added.]

161. One of ordinary skill in the art would have understood that the passage in Fact 160 is directed to a method of treating an allergy, not to a method of treating asthma. (Ex. 2001, ¶ 133; Ex. 2004, p. 53, lns. 18-25.).

162. In reference to the passage in Fact 160, there are no data or experiments disclosed in the Krieg '584 application which show that ISS alone, administered without antigen, was sufficient to treat or prevent allergy. (Ex. 2001 ¶134).

163. (Ex. 2001, ¶ 133; Ex. 2004, p. 53, lns. 18-25; Ex. 2042, p. 62, ln. 14 to p. 63, ln. 20; Ex. 2047, Title 1, Ch. 7).

***2. In vitro Data Of Krieg Application***

164. The *in vitro* experiments described in the Krieg specification provide an indicator that CpG containing nucleotides induce some type of an immune response that includes the production of certain cytokines such as Il-6 or IFN-gamma. (Ex. 2001, ¶¶ 160-161; Ex. 2004, pp. 43-52).

165. IL-6 is produced by many different types of cells – not just by T cells. (Ex. 2043, p. 62, lns. 1-15; Ex. 2050, Title 1, Ch. 7).

166. The presence of the cytokine IL-6 does not confirm that either a Th2 or Th1 cell produced the Il-6. (Ex. 2043, p. 63, ln. 14 – p. 64, ln. 24; Ex. 2050, Title 1, Ch. 7-8).

167. The presence of the cytokine IL-6 does not prove that there has been a shift in the immune response from Th2 to Th1. (Ex. 2043, p. 63, ln. 14 – p. 64, ln. 24; Ex. 2050, Title 1, Ch. 7-8).

168. The presence of IFN-gamma does not establish that there has been a shift from Th2 to Th1. (Ex. 2043, p. 67, lns. 3-11; Ex. 2050, Title 1, Ch. 8).

169. During cross-examination, Dr. Center testified that the mere presence of Th1 cytokines does not demonstrate that a shift from a Th2 to a Th1 immune response has occurred. (Ex. 2043, p. 67, lns. 3-11; Ex. 2050, Title 1, Ch. 8).

170. During cross-examination, Dr. Center testified as follows:

> 3 If interferon gamma is the hallmark Th1
> 4 cytokine, does the presence of interferon gamma
> 5 always indicate that there's been a shift from Th2
> 6 to Th1?
> 7 A. No. Gamma-interferon can be present in

8 multiple types of inflammatory reactions. In fact,
9 there are elevated levels of gamma-interferon in
10 certain allergic responses also, Th2 responses.
11 It's a balance. It's not an absolute. [Ex. 2043, p. 67, lns. 3-11; Ex. 2050, Title 1, Ch. 8].

171. The *in vitro* experiments described in the Krieg specification do not indicate or describe to one of ordinary skill in the art that the immunostimulatory nucleic acid containing a CpG motif causes a shift from Th2 to Th1. (Ex. 2001, ¶¶ 160-161; Ex. 2043, p. 65, lns. 17-21 and p. 67, lns. 3-11; Ex. 2050, Title 1, Ch. 8).

172. During cross-examination, Dr. Wallner testified that an animal model for asthma must be used to evaluate a method of treating asthma, not sole reliance on a cytokine profile. (Ex. 2042, p. 51, ln. 18 – p. 55, ln. 2 and p. 85, ln. 13 – p. 86, ln. 6; Ex. 2047, Title 1, Ch. 5-6; Ex. 2048, Title 1, Ch. 2).

173. During cross-examination, Dr. Center testified that "Th1 cytokines" are not necessarily exclusive to a Th1 response because the cytokines can be produced by non-Th1 cells. (Ex. 2043, p. 65, ln 1 – p. 67, ln. 11; Ex. 2050, Title 1, Ch. 8).

### *3. Krieg Claim 104 Is Not Supported By Krieg Patent Application Serial No 09/960,774*

174. Krieg is involved in the interference on the basis of U.S. Application No. 09/337,584 ("the Krieg Specification"), filed June 21, 1999. (Paper No. 1, p. 3; Ex. 2004).

175. The Krieg Specification has been accorded benefit for the purpose of priority of the October 30, 1997, filing date of U.S. Application No. 08/960,774 ("the '774 application"), which issued as U.S. Patent No. 6,239,116 on May 29, 2001; and the October 30, 1996, filing date of U.S. Application No. 08/738,652 ("the '652 application"), which issued as U.S. Patent No. 6,207,646 on March 27, 2001. (Paper No. 1, p. 5; Paper No. 22, p. 3, lns. 3-8).

176. In the Redeclaration of Interference dated March 14, 2007 (Redeclaration), the Administrative Patent Judge (APJ) withdrew Krieg's accordance of priority benefit of U.S. Patent Application No. 08/386,063, filed on February 7, 1995. (Paper No. 22, p. 2, lns. 2-5).

177. Considering the earlier-filed Krieg applications as a whole, one of ordinary skill in the art would not have considered Krieg to have been in possession of or to have disclosed how to practice a method of treating asthma comprising administration of an ISS without co-administration of an antigen. (Ex. 2001, ¶¶ 142, 148, 164, and 167).

178. The Krieg '774 and '652 Applications contain 13 Examples. (Ex. 2005, pp. 67-79; Ex. 2006, pp. 43-52).

179. Example 12 of the Krieg '774 and '652 Applications relates to a murine model of asthma. (Ex. 2001, ¶¶ 123, 141, and 152; Ex. 2004, p. 63, ln. 31 to p. 64, ln. 1; Ex. 2005, pp. 77-79; Ex. 2006, pp. 51-52).

180. Example 12 of the Krieg '774 and '652 Applications describes the administration of an ISS to one or more mice. (Ex. 2001, ¶¶ 124-128, 141, and 153-157; Ex. 2004, p. 11, lns. 27-32, p. 64, lns. 2-11 and 17-21, and Fig. 9; Ex. 2005, pp. 77-79; Ex. 2006, p. 10, ln. 35 to p. 11, ln. 2; p. 51, lns. 3-13 and 21-25, pp. 51-52, and Fig. 9).

181. Example 12 of the Krieg '774 and '652 Applications describe co-administration of an ISS and an antigen (*Schistosome* eggs) to mice. (Ex. 2001, ¶¶ 124-128, 141, and 153-157; Ex. 2004, p. 11, lns. 27-32; p. 64, lns. 2-11 and 17-21; Fig. 9; Ex. 2005, p. 77, ln. 16 to p. 78, ln. 3; Ex. 2006, p. 51, lns. 3-19 and 21-25, and Fig. 9).

182. Example 12 of the '774 and '652 Applications does not describe administration of an ISS to mice without co-administration of an antigen. (Ex. 2001, ¶¶ 129, 130, 141, 158, and 159; Ex. 2005, pp. 77-79; Ex. 2006, pp. 51-52).

183. Example 12 of the '774 and '652 Applications report that mice that were exposed to *Schistosome* eggs (antigen) without co-administration of ISS developed an acute inflammatory response in the lungs after airway challenge with SEA. (Ex. 2001, ¶¶ 124-128, 141, and 153-157; Ex. 2004, p. 11, lns. 27-32, p. 64, lns. 2-11 and 17-21, and Fig. 9; Ex. 2005, p. 78, lns. 12-15; Ex. 2006, p. 10, ln. 35 to p. 11, ln. 2, p. 51, lns. 3-13, and 21-25, p. 52, lns. 31-34, and Fig. 9).

184. Example 12 of the Krieg '774 and '652 Applications report that co-administration of eggs (antigen) and ISS almost completely abolished the increase in eosinophils in the lungs after airway challenge with SEA. (Ex. 2001, ¶¶ 124-128, 141, and 153-157; Ex. 2004, p. 11, lns. 27-32, p. 64, lns. 2-11 and 17-21, and Fig. 9; Ex. 2005, p. 78, lns. 15-17; Ex. 2006, p. 10, ln. 35 to p. 11, ln. 2, p. 51, lns. 3-13, and 21-25, p. 52, lns. 34-37, and Fig. 9).

185. Example 12 of the Krieg '774 and '652 Applications do not report any data relating to an immunological response to an airway challenge with SEA wherein an ISS was previously administered to mice without co-administration of an antigen. (Ex. 2001, ¶¶ 129, 130, 141, 158, and 159; Ex. 2005, pp. 77-79; and Ex. 2006, pp. 51-52).

186. One of ordinary skill in the art would not have considered Example 12 of the Krieg '774 or '652 Applications to convey a method of treating asthma comprising administration of an ISS without co-administration of an antigen. (Ex. 2001, ¶¶ 129, 130, 141, 158, and 159; Ex. 2005, pp. 77-79; Ex. 2006, pp. 51-52).

187. On page 10, lines 18-22 of the Krieg '774 application, Krieg states:

> Furthermore, by redirecting a subject's immune response from Th2 to Th1, the claimed nucleic acid sequences can be used to treat or prevent an asthmatic disorder. In addition, the claimed nucleic acid molecules can be administered to a subject in conjunction with a particular allergen as a type of desensitization

> therapy to treat or prevent the occurrence of an allergic reaction associated with an asthmatic disorder. [Ex. 2005, p. 10, lns. 18-22].

188. On page 8, lines 13-17 of the Krieg '652 application, Krieg states:

> Further, by redirecting a subject's immune response from Th2 to Th1, the instant claimed nucleic acid molecules can be administered to treat or prevent the symptoms of asthma. In addition, the instant claimed nucleic acid molecules can be administered in conjunction with a particular allergen to a subject as a type of desensitization therapy to treat or prevent the occurrence of an allergic reaction. [Ex. 2006, p. 8, lns. 13-17].

189. One of ordinary skill in the art would have understood the first sentence of the passages in Facts 187 and 188 to disclose the general concept of administering an ISS to treat or prevent an asthmatic disorder, such as allergic or non-allergic asthma. (Ex. 2001, ¶¶ 120, 141, and 150; and Ex. 2006, p. 8, lns. 13-17).

190. One of ordinary skill in the art would have understood the first sentence of the passages in Facts 187 and 188 to convey a recognition that allergic disorders were considered to be associated with Th2 responses and that ISS compounds were known to redirect an immune response from a Th2 to a Th1 response. (Ex. 2001, ¶¶ 120, 141, and 150; and Ex. 2006, p. 8, lns. 13-17).

191. One of ordinary skill in the art would not have considered the first sentence of the passage in Facts 187 and 188 to describe any specific method of administering ISS to treat or prevent asthma. (Ex. 2001, ¶¶ 120, 141, and 150; and Ex. 2006, p. 8, lns. 13-17).

192. One of ordinary skill in the art would have understood the second sentence of the passage in Facts 187 and 188 as additionally noting that, in the context of allergic asthma, the co-administration of an ISS with an asthma-stimulating antigen could be used to desensitize a subject to treat or prevent the occurrence of an allergic reaction associated with an asthmatic disorder. (Ex. 2001, ¶¶ 121, 141, and 151).

193. The earlier-filed Krieg applications provide the following disclosure:

> In general, it appears that allergic diseases are mediated by Th2 type immune responses and autoimmune diseases by Th1 immune response. Based on the ability of the immunostimulatory nucleic acid molecules to shift the immune response in a subject from a Th2 (which is associated with production of IgE antibodies and allergy) to a Th1 response (which is protective against allergic reactions), an effective dose of an immunostimulatory nucleic acid (or a vector containing a nucleic acid) alone or in conjunction with an allergen can be administered to a subject to treat or prevent an allergy. [Ex. 2005, p. 66, lns. 3-9; Ex. 2006, p. 41, lns. 22-29; Emphasis added].

194. One of ordinary skill in the art would have understood that the passage in Fact 193 is directed to a method of treating an allergy, not a method of treating asthma. (Ex. 2001, ¶¶ 133, 141, and 162; Ex. 2004, p. 53, lns. 18-25; and Ex. 2006, p. 41, lns. 22-29).

195. One of ordinary skill in the art would have understood that while an "allergy" and "asthma" can have similar pathologies, a method of treating an allergy will not necessarily provide a method of treating asthma. (Ex. 2001, ¶¶ 135, 136, 141, 164, and 165; Ex. 2006, 2008-2010; Ex. 2017, pp. 332-335).

196. In many cases, the medications or treatment given to patients with asthma are different from those used in patients with allergy. (Ex. 2001, ¶¶ 135, 141, and 164; and Ex. 2017, pp. 332-335).

197. One of ordinary skill in the art evaluating a proposed method of treating asthma, especially a method involving the use of an ISS to redirect a Th2 to Th1 response, would not have concluded that the proposed method of treatment is effective without evaluating experimental data that is indicative of such an effect. (Ex. 2001, ¶¶ 135, 141, and 164; and Ex. 2017, pp. 332-335).

198. One of ordinary skill in the art would not have considered the passages cited in Facts 187, 188, and 193 to convey that Krieg was in possession of or taught how to practice a

method of treating asthma comprising the administration of an ISS without co-administration of an antigen. (Ex. 2001, ¶¶ 135, 141, and 164; and Ex. 2017, pp. 332-335).

199. The earlier-filed Krieg applications refer to the use of ISS compounds in the context of the treatment of asthma:

> Nucleic acids containing unmethylated CpG motifs may also have significant therapeutic utility in the treatment of asthma. Th2 cytokines, especially IL-4 and IL-5 are elevated in the airways of asthmatic subjects. These cytokines promote important aspects of the asthmatic inflammatory response, including IgE isotype switching, eosinophil chemotaxis and activation and mast cell growth. Th1 cytokines, especially IFN-γ and IL-12, can suppress the formation of Th2 clones and production of Th2 cytokines. [Ex. 2005, p. 66, lns. 10-15; Ex. 2006, p. 41, lns. 31-36].

200. One of ordinary skill in the art would have understood the passage in Fact 199 to disclose the possibility that an ISS may have utility in the treatment of asthma in view of the observation that asthmatic subjects have elevated levels of Th2 cytokines in their airways and that Th1 cytokines (induced by an ISS) can suppress the production of Th2 cytokines. (Ex. 2001, ¶¶ 118, 141, and 148).

201. One of ordinary skill in the art would not have considered the passage in Fact 199 to convey that Krieg was in possession of or taught how to practice a method of treating asthma comprising the administration of an ISS without co-administration of antigen. (Ex. 2001, ¶¶ 118, 141, and 148).

### D. Krieg Failed to Conduct a Proper Analysis of Patentability of its Claims under 35 U.S.C. § 135(b)(1)

202. U.S. Patent No. 6,498,148 to Raz ("the '148 patent") issued on December 24, 2002. (Ex. 2003, p. 1).

203. The critical date for purposes of 35 U.S.C. § 135(b)(1) with respect to the Raz '148 patent is December 24, 2003. (Ex. 1054, pp. 3-5).

204. Krieg presented claims 60 and 76 in the involved '584 application in a Preliminary Amendment dated June 21, 1999. (Ex. 1054, pp. 3-4).

205. Krieg claim 60, presented in a Preliminary Amendment in the '584 application, is directed to a "method for desensitizing a subject against the occurrence of an allergic reaction...." (Ex. 1054, p. 3).

206. Claim 104 is silent regarding the administration of antigen. (Ex. 1050, p. 6).

207. During cross-examination, Dr. Center testified as follows:

21 Q. So in your view, is there a distinction
22 between an allergy and asthma?
23 A. The hallmark of asthma is airway
24 hyperreactivity. The most common type of asthma is

1 allergic, but there are types of asthma for which
2 there is no allergic component or none that is
3 identified. [Ex. 2043, p. 38, ln. 21 – p. 39, ln. 3; Ex. 2050, Title 1, Ch. 4]

208. During cross-examination, Dr. Schleimer testified as follows:

2 Q Are you aware of any allergens which
3 produce responses other than Th2 responses?
4 A As I said, allergy is a term used to
5 describe a large number of different syndromes, most
6 of which are Th2 and IgE mediated, but many which
7 are not.
8 Q What are examples of ones which are not?
9 A For instance, drug allergies, penicillin
10 allergies. They're not necessarily IgE mediated or
11 Th2 mediated.
12 Q Okay. So if we exclude those particular
13 allergies, this sentence in paragraph 25 then would
14 refer to any allergy that was IgE or Th2 mediated.
15 Would that be correct?
16 A Yes.
17 Q And that would include allergic asthma?
18 A For the most part.
19 Q And it may include nonallergic asthmas as
20 well?
21 A Inasmuch as there's a similarity between

22 the T-cell cytokines and Th2 in nonallergic asthma. [Ex. 2046, p. 29, lns. 2-22].

209. During cross-examination, Dr. Wallner testified as follows:

16 Q. Do you understand that the Krieg claims
17 are directed to a method of treating allergies in
18 this interference?
19 A. Yes. And asthma, allergic asthma.
20 Q. Is there a difference between -- would one
21 of ordinary skill in the art consider there to be a
22 difference between an allergy and allergic asthma?
23 A. You can have an allergy without having
24 allergic asthma. [Ex. 2042, p. 15, lns. 16-24; Ex. 2047, Title 1, Ch. 1]

210. Desensitization therapy involves repeatedly administering small quantities of an allergen over time to build up a tolerance to the allergen with the objective of reducing the allergic response to subsequent exposure to the allergen, the advantages of which, in the treatment of allergy, is its interference with the mechanisms responsible for biological mediator release. (Ex. 2016, p. 19.19).

211. Dr. Wallner testified that "desensitization therapy, is geared toward down-regulating those T cells that respond to the allergen, and therefore decreasing the allergic responses, the Ig production." (Ex. 2042, p. 49, lns. 17-20; Ex. 2047, Title 1, Ch. 5).

212. In the Second Declaration of David M. Center, M.D. In Support of Krieg Substantive Motions, Dr. Center defined desensitization therapy as a therapy involving "repeated administration of an allergen to a subject in order to tolerize the subject to the allergen. Subjects undergoing desensitization therapy, including allergic asthmatic subjects, are administered antigen (or allergen)." (Ex. 1051, ¶ 28).

213. Dr. Center testified that desensitization means the "gradual administration of an antigen to which you've been sensitized in a stoichiometric fashion, such that all of the antigen-

specific receptors are occupied on the cells that are involved in the immune response." (Ex. 2043, p. 39, ln. 23 to p. 40, ln. 3; Ex. 2050, Title 1, Ch. 4).

214. During cross-examination, Dr. Center testified as follows: "...desensitization which is better termed immunotherapy. And by immunotherapy, we mean the gradual administration of a -- increasing doses of an antigen to which you're specific -- you're sensitized, thereby inducing a different type of immune response, which either inhibits or blocks the allergic response; that's allergy shots in common parlance." (Ex. 2043, p. 40, lns. 11-18; Ex. 2050, Title 1, Ch. 4).

215. During cross-examination, Dr. Center testified as follows:

... the strictest definition of desensitization is a gradual administration of an antigen to which you've been sensitized in a stoichiometric fashion, such that all of the antigen-specific receptors are occupied on the cells that are involved in the immune response.

That antigen receptor, ligand-receptor interaction is temporary, and once you cease exposure to that antigen, you then are sensitive again; that's what we call drug desensitization. For example, if you were allergic to penicillin, I can safely give you penicillin via that mechanism.

There's another term which some people also use for desensitization which is better termed immunotherapy. And by immunotherapy, we mean the gradual administration of a -- increasing doses of an antigen to which you're specific -- you're sensitized, thereby inducing a different type of immune response, which either inhibits or blocks the allergic response; that's allergy shots in common parlance.

Q. And that's -- that involves the deliberate administration of whatever particular antigen you're attempting to desensitize the subject to; is that correct?

A. In that form, yes.

[Ex. 2043, p. 39, ln. 21 to p. 40, ln. 23; Ex. 2050, Title 1, Ch. 4].

**E. Krieg's Claims 104 and 105 Do Not Interfere with Raz's Claims**

216. Krieg Claim 104 is directed to a generic method of treating asthma. (Ex. 1050, p. 6).

217. Krieg Claim 104 does not recite a method of treating asthma "wherein the immunostimulatory polynucleotide does not comprise a nucleotide sequence encoding the antigen." (Ex. 1050, p. 6).

218. Krieg Claim 104 does not recite a method of treating asthma "wherein the immunostimulatory polynucleotide is administered without the antigen, including without a polynucleotide encoding the antigen." (Ex. 1050, p. 6).

219. Krieg Claim 105 is directed to a method of treating asthma and further limits claim 104 by reciting that the claimed method comprises "administering the allergen." (Ex. 1050, p. 6).

220. Krieg Claim 105 does not recite a method of treating asthma "wherein the immunostimulatory polynucleotide does not comprise a nucleotide sequence encoding the antigen." (Ex. 1050, p. 6).

221. Krieg Claim 105 does not recite a method of treating asthma "wherein the immunostimulatory polynucleotide is administered without the antigen, including without a polynucleotide encoding the antigen." (Ex. 1050, p. 6).

222. Krieg Claims 104 and 105 do not suggest the limitation of a method of treating asthma "wherein the immunostimulatory polynucleotide does not comprise a nucleotide sequence encoding the antigen." (Ex. 2001, ¶¶ 103-106; Ex. 2008, p. 380A, col. 2; Ex. 2009, p. 282A, col. 1; and Ex. 2010, pp. 2257-2258).

223. Krieg Claims 104 and 105 do not suggest the limitation of a method of treating asthma "wherein the immunostimulatory polynucleotide is administered without the antigen, including without a polynucleotide encoding the antigen." (Ex. 2001, ¶¶ 103-106; Ex. 2008, p. 380A, col. 2; Ex. 2009, p. 282A, col. 1; and Ex. 2010, pp. 2257-2258).

224. At column 2, lines 43-50 of the involved Raz '148 patent, Raz states the following:

> Unlike canonical immunotherapy, immunity is stimulated by this method of the invention ***even when no additional antigen is introduced into the host.*** Thus, use of the method to boost the immune responsiveness of a host to subsequent challenge by a sensitizing antigen ***without immunization*** avoids the risk of immunization-induced anaphylaxis, suppresses IgE production in response to the antigen challenge ***and eliminates the need to identify the sensitizing antigen for use in immunization.***" [Ex. 2003, col. 2, lns. 43-50; Emphasis added].

225. In 1996-1999, one of ordinary skill in the art would have expected that a method of treating an asthmatic subject by the administration of an ISS would involve co-administration of the particular asthma-stimulating antigen to treat the asthmatic subject. (Ex. 2001, ¶ 103).

226. In 1996-1999, one of ordinary skill in the art would have considered a method of treatment of asthma using an ISS without the co-administration of an antigen to be a significant achievement. (Ex. 2001, ¶ 103).

227. In September 1996, Drs. Kline and Krieg, the named inventors on the involved Krieg application, published an Abstract titled "CpG Motif Oligonucleotides are Effective in Prevention of Eosinophilic Inflammation in a Murine Model of Asthma" ("the Kline '96 Abstract"). (Ex. 2008, p. 380A, col. 2).

228. The Kline '96 Abstract indicated that Th2 cytokines were known to be associated with the development of eosinophilia and inflammation in asthma. (Ex. 2001, ¶ 58; and Ex. 2008, p. 380A, col. 2).

229. The Kline '96 Abstract described an experiment wherein an ISS and *Schistosome* eggs were co-administered to mice, followed by airway challenge with SEA. The results showed a decrease in eosinophil levels. (Ex. 2001, ¶ 60; and Ex. 2008, p. 380A, col. 2).

230. The experiment in the Kline '96 Abstract established that when ISS is co-administered with antigen (*i.e.*, with *Schistosome* eggs), an immune response to subsequent SEA airway challenge was reduced. (Ex. 2001, ¶ 60; and Ex. 2008, p. 380A, col. 2).

231. The Kline '96 Abstract describes an experiment wherein ISS was administered "alone." (Ex. 2008, p. 380A, col. 2).

232. The Kline '96 Abstract states "[s]ystemic administration of the oligonucleotide...alone did not result in any significant change in BAL cellularity..." (Ex. 2008, p. 380A, col. 2; Emphasis added).

233. One of ordinary skill in the art would have interpreted the Kline '96 Abstract to describe either: (a) a control wherein ISS was administered to non-sensitized mice, the mice were not airway challenged and then BAL cellularity was evaluated; or (b) administration of an ISS that was not effective in decreasing BAL cellularity if the ISS was not co-administered with the antigen. (Ex. 2001, ¶¶ 62 and 63; and Ex. 2008, p. 380A, col. 2).

234. In 1997, Drs. Kline and Krieg published an Abstract titled "Immune Redirection by CpG Oligonucleotides: Conversion of a Th2 Response to a Th1 Response in a Murine Model of Asthma" ("the Kline '97 Abstract"). (Ex. 2009, p. 282A, col. 1).

235. The Kline '97 Abstract reported testing a hypothesis that administration of ISS may decrease the eosinophilic response in asthmatic inflammation. (Ex. 2009, p. 282A, col. 1).

236. To test the hypothesis, the Kline '97 Abstract described using a murine model of asthma, wherein mice were sensitized to *Schistosome* eggs and subsequently challenged with SEA. (Ex. 2001, ¶ 68; and Ex. 2009, p. 282A, col. 1).

237. The Kline '97 Abstract described a group of mice were not administered ISS. (Ex. 2001, ¶ 69; and Ex. 2009, p. 282A, col. 1).

238. The Kline '97 Abstract described administering ISS and *Schistosome* eggs to mice, followed by subsequent airway SEA challenge. Kline reported that airway eosinophilia was significantly decreased, to $0.53 \pm 0.11 \times 10^6$ eosinophils. (Ex. 2001, ¶ 70; Ex. 2009, p. 282A, col. 1).

239. One of ordinary skill in the art would have understood the experiment described in the Kline '97 Abstract to demonstrate that when ISS is co-administered with *Schistosome* eggs, immune response to subsequent antigen challenge decreased. (Ex. 2001, ¶ 70; Ex. 2009, p. 282A, col. 1).

240. The Kline '97 Abstract reported that "CpG ODN co-administered with *Schistosome* eggs (but not CpG ODN alone) lead to decreased airway eosinophilia following subsequent airway challenge with SEA." (Ex. 2009, p. 282A, col. 1).

241. One of ordinary skill in the art would have interpreted the Kline '97 Abstract to describe either: (1) a control experiment which demonstrates that the CpG ODN did not appear to effect airway eosinophilia or (2) that when ISS was administered to sensitized mice, without co-administration of antigen, Kline did not observe any decreased airway eosinophilia following subsequent SEA challenge using such methodology. (Ex. 2001, ¶ 72; Ex. 2009, p. 282A, col. 1).

242. Kline et al. published a Paper titled "Cutting Edge: Modulation of Airway Inflammation by CpG Oligodeoxynucleotides in Murine Model of Asthma" ("the Kline '98

Paper") that was received for publication on November 26, 1997, and accepted for publication on January 14, 1998. (Ex. 2010).

243. The Kline '98 Paper examined the effects of ISS in a murine model of asthma. In this model, mice were sensitized to *Schistosome* eggs and challenged with SEA. To determine the effects of ISS on the development of airway eosinophilia, Kline et al. performed whole lung lavage on mice that received *Schistosome* eggs in the presence or absence of CpG ODN, control ODN or a saline control, and then later challenged with SEA. (Ex. 2001, ¶¶ 76-77; Ex. 2010, p. 2555, col. 2, first full ¶; and p. 2556, col. 2, first full ¶).

244. The Kline '98 Paper reported that sensitized mice (which were sensitized by administration of *Schistosome* eggs), followed by SEA airway challenge showed the highest eosinophil count. (Ex. 2001, ¶ 80; Ex. 2010, p. 2556, col. 1, first ¶; col. 2, first full ¶; and Fig. 1).

245. The Kline '98 Paper reported a comparison of mice that were co-administered control ODN and *Schistosome* eggs with mice that were co-administered ISS and *Schistosome* eggs. Both groups of mice were subsequently challenged with SEA. (Ex. 2001, ¶ 80; Ex. 2010, p. 2556, col. 1, first ¶; col. 2, first full ¶; and Fig. 1).

246. The Kline '98 Paper reported that results from whole lung lavage showed a decrease in eosinophil counts in the mice that were co-administered ISS and *Schistosome* egg as compared to the groups that were co-administered with *Schistosome* eggs and control ODN. (Ex. 2001, ¶ 80; Ex. 2010, p. 2556, col. 1, first ¶; col. 2, first full ¶; and Fig. 1).

247. The experiment in the Kline '98 Paper established that ISS co-administered with an antigen, can reduce antigen-induced airway inflammation and protect against asthma. (Ex.

2001, ¶¶ 76, 78, 80, and 83; Ex. 2010, p. 2555, col. 2, first full ¶; p. 2556, col. 1, first ¶ and col. 2, first full ¶; p. 2557, col. 1, last ¶ to p. 2558, col. 1, 1st ¶; and Figs. 1 and 5).

248. The Kline '98 Paper reported that "CpG ODN alone do not offer significant protection against the development of airway inflammation." (Ex. 2010, sentence bridging pp. 2557-2558; Emphasis added).

249. The Kline '98 Paper did not offer data which illustrates the result of mice having been administered ISS, without co-administration of an antigen. (Ex. 2001, ¶ 83; Ex. 2010, p. 2557, col. 1, last ¶ to p. 2558, col. 1, 1st ¶; and Fig. 5).

250. The Kline '98 paper reads as follows:

> In addition, these effects are Ag specific; in other studies (not shown), CpG ODN can protect against the development of eosinophilic airway inflammation in an OVA murine model of asthma, but protection against OVA sensitization does not confer protection against schistosome sensitization. [Ex. 2010, p. 2558, col. 1, lns. 1-6].

251. One of ordinary skill in the art would have understood the Kline '98 Paper as reporting that CpG ODN administered to mice and subsequently airway challenged with SEA did not offer significant protection against development of airway inflammation. (Ex. 2001, ¶ 83; Ex. 2010, p. 2557, col. 1, last ¶ to p. 2558, col. 1, 1st ¶; and Fig. 5).

252. During cross-examination, Dr. Center testified that "because the art of treatment, at that time and currently, frequently involves the administration of antigen, as in traditional immunotherapy or allergy shots, and so it would not be logical to exclude one very valuable potential therapy..." (Ex. 2043, p. 50, lns. 15-20; Ex. 2050, Title 1, Ch. 6).

## CERTIFICATE OF FILING

The undersigned certifies that a copy of the paper entitled "**RAZ OPPOSITION 4**" and its Appendices 1-3 were filed with The Board of Patent Appeals and Interferences this 10th day of September, 2007, by uploading them onto the Interference Web Portal, located at:

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September 10, 2007

/Oliver R. Ashe, Jr./
Oliver R. Ashe, Jr.